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June

THIRTY-SIXTH MEETING

ADVISORY COMMITTEE TO THE DIRECTOR, NIH
June 15-16, 1978

U.S NATIONAL INSTITUTES OF HEALTH
Bethesda, Maryland
Building 31, Conference Room 10C

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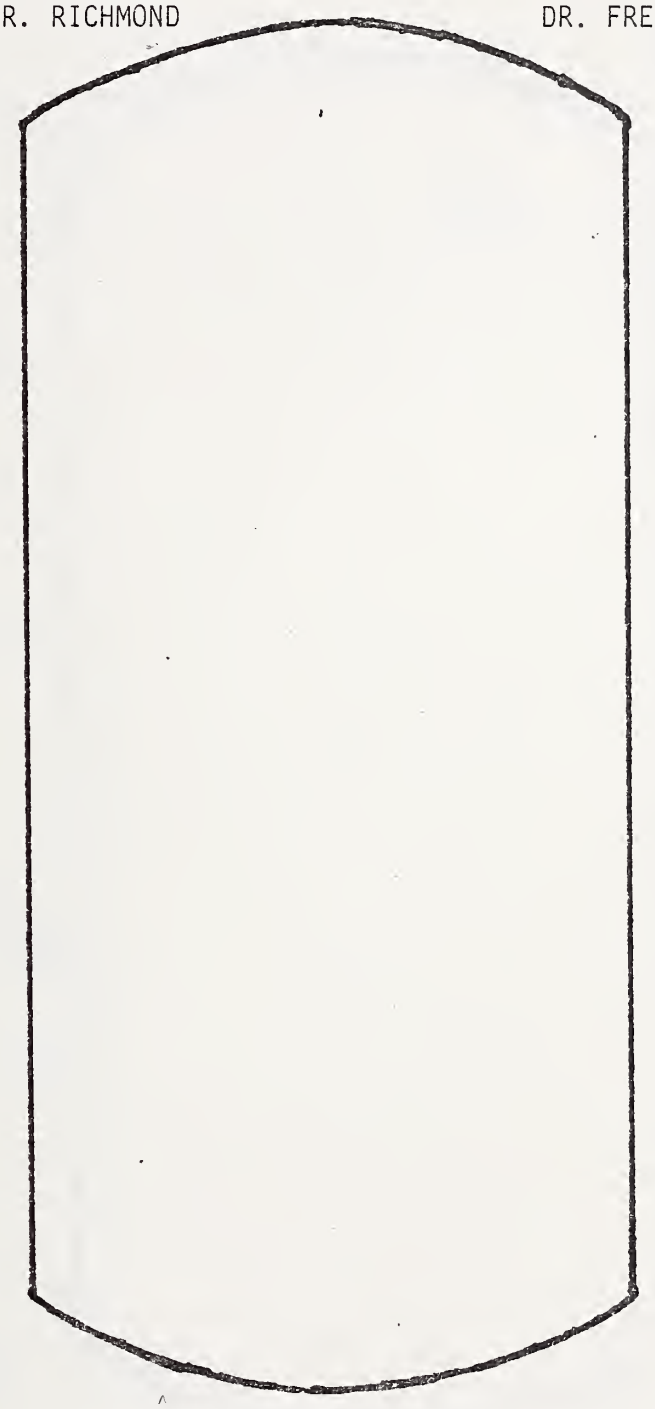
MEETING OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH
BUILDING 31, CONFERENCE ROOM 10C
June 15-16, 1978



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Mrs. Jacqueline Wexler
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NEW MEMBER, DAC

DR. FREDRICKSON

Revised June 12, 1978

AGENDA

THIRTY-SIXTH MEETING OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH
June 15-16, 1978
Building 31, Conference Room 10
National Institutes of Health

THURSDAY, June 15

9:00 a.m.	Opening Remarks	Dr. Fredrickson Dr. Richmond, ASH
9:30	Attracting and Nurturing Young Scientists	
	Director's Advisory Committee	Dr. Bondurant
	Consultant	Dr. Neurath
	Government	Dr. Klerman, ADAMHA
10:00	Committee Questions and Discussion	
10:30	Coffee Break	
10:45	Clinical Applications/Health Services	
	Director's Advisory Committee	Dr. Bennett
	Consultant	Dr. Marks
11:15	Committee Questions and Discussion	
11:45	Fundamental Research	
	Director's Advisory Committee	Dr. Comroe
	Consultant	Dr. Tosteson
	Consultant	Dr. Palade
12:15 p.m.	Committee Questions and Discussion	
12:45	Lunch	
2:00	Regulatory Needs	
	Director's Advisory Committee	Dr. Udenfriend
	Consultant	Dr. Melmon
	Government	Mr. Jellinek, EPA Dr. Miller, FDA
2:30	Committee Questions and Discussion	
3:15	Coffee Break	

3:30 p.m. General Overview

Director's Advisory Committee	Dr. Eisenberg Dr. Wildavsky Mr. Hutt
Consultant	Dr. Robbins
Government	Dr. Smith, HCFA Dr. Omenn, OSTP

4:30 Committee Questions and Discussion

Hans Nawrath + Geo. Galade.

5:15 Adjourn

FRIDAY, June 16

9:00 a.m. Opening Remarks . . . . . Dr. Fredrickson

9:15 Committee Members' Opinions (5 min. each)

10:30 Coffee Break

10:45 Policy Regarding Recombinant DNA Research . . . . . Dr. Fredrickson

11:15 Committee Questions and Discussion . . . . . Dr. Fredrickson

12:00 Adjourn

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June 1978

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ADVISORY COMMITTEE TO THE DIRECTOR, NIH

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20201

OFFICE OF THE SECRETARY

As Delivered

REMARKS OF

SECRETARY JOSEPH A. CALIFANO, JR.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

ANNUAL MEETING OF

THE AMERICAN FEDERATION FOR CLINICAL RESEARCH

San Francisco Hilton Hotel

San Francisco, California

April 29, 1978

I have come across the country to pay tribute to you -- and to signal the commitment of this Administration to the vital research enterprise you represent: a commitment that the President is determined to express not only in words, but in deeds.

In the process, I want to discuss a subject of intense interest to you and to me: the future of Federal support for health research.

I want to suggest an important new process that we in government and you in the research community should begin to support basic research: development, for the first time, of a multi-year strategy to guide allocation of limited government health research dollars.

I hope you will not think it presumptuous for a layman to propose a new strategy for a subject on which you are so well informed. Let me say in my defense that though I may be a new student of the issues in science and biomedical research, since January 1977 I have been getting a crash course.

I had scarcely taken office as Secretary of HEW when I was immersed in the ongoing controversy about the effectiveness and safety of Swine flu vaccine.

Since then my trial by fire has continued from one issue to another in which science, medicine, politics, religion, ethics, and human values either converge or collide, in ways all too familiar to you:

- Abortion
- Saccharin
- Psychosurgery
- Fetal Research
- Recombinant DNA

Just this week, based on research into the dangers posed by asbestos, we launched a public information campaign to warn past workers of the health risks they face from asbestos exposure.

What have I learned from fifteen months of all this? Several things.

I have learned how critical it is to have a firm core of scientific knowledge upon which to base policy decisions. When I launched the Department's anti-smoking campaign, I knew it would arouse controversy, but I also knew that the effort was soundly and firmly based on painstaking and convincing scientific research.

I have learned the importance of working out, what Don Fredrickson calls, "technical consensus" on controversial scientific issues -- and of doing so in the open, not behind closed doors. When I was faced with difficult questions of immunization policy -- not the least of which were lack of public confidence as a result of the Swine flu program -- we held important meetings in the open and solicited a broad range of scientific and technical advice in an effort to find a common ground of expertise upon which to build. When I eventually made my decisions, the public knew everything I knew and was thus better able to judge them.

And I have learned that at the core of many health problems and controversies that government must resolve today is the dilemma created by enormous and pressing needs and limited resources. Indeed, in no other field is that dilemma more sharply posed -- or more important to resolve -- wisely and fairly -- than in health, and health research.

The Federal government has become the dominant force in biomedical research not only in this country, but increasingly, throughout the world.

It supports the largest health research establishment in the world today. HEW's support for health research amounted to an estimated $3.4 billion in 1977 -- over 60 percent of the nation's total expenditure for such research, and almost 80 percent of the Federal health research effort.

The National Institutes of Health today oversee a research budget of $2.7 billion in support of 15,000 principal investigators including 13,000 research grantees in non-federal institutions.

These are impressive numbers -- and all the more impressive when we reflect that they represent a relatively recent development. The Federal Health Research enterprise has existed for less than a generation.

In that brief span, we have realized some significant achievements -- achievements with which you are intimately familiar and for which you are largely responsible: unraveling the mechanisms of heredity; gains against rheumatic heart disease, hypertension, and rubella; new medicines derived from better understanding of the chemical basis for communication in the nervous system; the Salk and Sabin polio vaccines.

Each of these achievements reveals the march of our national health effort in just the right cadence, from basic research to applied research to technology transfer.

It is important, I think, to dwell upon these accomplishments; they are important justifications -- though hardly the only ones -- for our large research investments: justifications that the American people can easily grasp.

Yet, though the vital signs for our research enterprise remain good, some danger signals have appeared in recent years. As you well know, the

great expansion of the National Institutes of Health took place between 1955 and 1968, and not in the decade since then.

Last July, President Carter ordered a thorough-going review of Federal support for basic research. It turned up some sobering facts:

- Over the past ten years, Federal support for basic research has declined by nineteen percent in constant dollars;
- The quality of scientific plant and equipment at our great institutions has badly deteriorated;
- Research opportunities for young university scientists have been declining -- and so the percentage of young scientists on our faculties declined from 43 percent in 1968 to 27 percent in 1975: a chilling omen for future scientific achievement.

In the health field, there were, for example, serious efforts in the early 1970s to cut back on funding for biomedical research, under the guise of containing health expenditures.

It was foolish to think that we could make significant savings by cutting back biomedical research. The total spent for biomedical research, after all, is less than four percent of our nation's health expenditures. Contrast that with the 40 percent spent -- too often profligately -- on hospital care and the additional 20 percent spent on professional fees.

Realizing this, and deeply concerned about the nation's future research capacity, President Carter last fall determined that we should halt this downward drift and reverse it. The President directed a new emphasis on basic research in Federally supported science programs. The President's

fiscal 1979 budget for NIH contains a direction to reprogram $93 million more to basic research.

This move to begin to redress the research balance is a significant step. It represents a commitment that is an important part of my message to you today. And the state of the research enterprise remains good, even if the growth spurt of a decade ago is not likely to recur soon.

The size and quality of the program for this meeting attest to the vigor of current medical research in this country. The excellence of our health research is also evidenced by the frequency with which Americans win the Nobel prize for medicine or physiology. In the last two years, five Americans received this award.

Thus, the President's commitment to basic research and the present stability of your efforts are encouraging indicators. But every day brings home more forcibly to us in government the limits on our resources -- limits on the amount of basic research, limits on the ability of research to help with some of the truly gargantuan health problems facing the nation -- limits that will be with us for the foreseeable future.

In an era in which resources for basic research are limited, we must develop a better strategy to guide the allocation of the federal research dollar. A multi-year plan will serve to level out the annual appropriations fluctuations that make rational research planning so difficult.

It is for this fundamental reason that I want you to help me set in place a new process by which HEW can develop a multi-year plan for health research.

At present, we do have decisions -- often made well -- about allocating funds within particular disciplines, or specific, relatively narrow areas of concern. But we do not have an across-the-board strategy for health research that assesses research and health needs in a systematic and comprehensive way.

Too often -- and I recognize that we in the Executive Branch, as well as those in Congress, are hardly free from blame -- our research dollars may go to popular causes, to the disease of the month, rather than to scientifically important endeavors. Too often, our research dollar may be overconcentrated in particular areas at the expense of other, equally valid and important spheres of inquiry. Too often, we do not ask whether our health research effort bears a reasonable relationship to the basic burden of illness in America -- including mortality, disability, and cost.

A multi-year strategy for basic health research, covering at least five years, is, in my judgment, an extraordinarily important goal:

- Such a plan will help us all, especially those of us in Government, resist some of the inevitable but not always desirable pressures that attend the distribution of substantial research dollars.
- Such a plan will bring an important measure of stability to the research enterprise by pointing out broad directions of government support for a more extended and realistic period of time than next year's budget cycle.
- Such a plan, by focusing on the important relationship between health research and health needs, will encourage

the creative interaction of ideas -- from the laboratory to the systems of health prevention, delivery, and regulation and from those systems back to the laboratory -- that will enrich the process of research itself.

- Such a plan will help us to tune our research efforts so that they bear an appropriate relationship to our nation's health needs.

It is far easier, I know, to agree upon the need for a strategy than to agree upon a strategy itself. For some, the mere mention of a five-year strategy, or any sort of strategy, may raise fears of well-intentioned but bureaucratic official interference with science.

I am acutely sensitive to this concern. And I am persuaded that development of a five-year research strategy will enhance, not diminish, the research effort. I also believe that the process by which we arrive at such a strategy is almost as important as the strategy itself.

Obviously, such a process should be conducted in the open, with full and robust discussion. We intend to seek advice and counsel from all quarters -- first and foremost from you, the leaders of the health research community, as well as from other interested parties. And we will, of course, consult fully with members of the Congress.

But the process will also be conducted with great care and deliberation. To that end, I envision the following steps in developing the five-year research plan.

- During the next three months, we will seek from all appropriate parties suggestions about the basic principles

that should inform the development of the plan. I have asked Dr. Fredrickson to develop and implement the most effective system for obtaining suggestions. This initial process of gathering and debating appropriate principles will include a conference on health research planning to be held at the National Institutes of Health this summer.

- After this initial consultation with the concerned communities, we will publish a tentative statement of the principles next fall and then seek extensive comments and criticisms before publishing the final principles early in 1979.
- During 1979, we will develop a more complete plan by, again, seeking advice, publishing a tentative plan, and then soliciting additional comments and criticisms -- with early 1980 as a target date for completion.

I recognize that as this process moves forward there will be intense debate. But that kind of debate and reassessment, in public, of the government-funded health research effort will, I am sure, be a stimulant, not a corrosive.

Indeed, I am confident that an energetic exchange of ideas among the research community, the government, the medical profession, consumers of medical services and others -- given a sharp focus by the objective of developing a multi-year plan to guide distribution of our limited research dollars -- will not only be novel, it will be of substantial benefit to all involved.

To give you a flavor of what I envision, let me share with you several tentative principles that might underlie a five-year plan. The first three principles are hardly controversial, but the two that follow, while perhaps unexceptionable in phrasing, may well be controversial in application. These principles are merely illustrative, and are neither immutable nor exhaustive.

- The most basic principle in my judgment should be this: to maintain at a high level and to enhance our support for fundamental research into biology and behavior.

The building of our current capacity represents a 25-year investment by the American people. It would be folly to jeopardize the network of competent investigators and institutions created so painstakingly over the years.

We intend to do everything in our power to strengthen this vital national commitment to knowledge development.

As we maintain our support for health research we should recognize several important dimensions of this principle:

-- There must be freedom to pursue research topics that are not immediately relevant, for basic research is nothing less than a long-term investment and we cannot program or order neatly the mysterious and serendipitous ways in which new knowledge is developed.

-- There must be diversity in the research that we support. The population-based life-sciences -- biostatistics, epidemiology, various behavioral sciences -- are at least

as basic to our understanding of health as the more affluent and popular consumers of research dollars, biochemistry and molecular genetics.

-- Another important dimension of this first principle is that serious attention must be given to renewal of the physical research plant, in addition to support for the scientists who seek to advance human knowledge. This plant is deteriorating and obsolescing. As the University Presidents' report on Research Universities and the National Interest stated: "The most serious reduction [in Federal support] has occurred in funds for new equipment and facilities and for upgrading existing plant." We must reverse that trend.

- A second principle is that we must assure that there are amole opportunities for young investigators.

We must consciously find ways to nourish the development of -- and provide research opportunities for -- the "Young Squirts." If research is to flourish, then we must appropriately structure competition between, as well as within, the generations -- for that competition has, so often in the past, been the driving, creative force in knowledge expansion.

- Third, basic research has to be accompanied by vigorous, thoughtful and, where appropriate, interdisciplinary applications.

Seeking important uses for the fundamental knowledge developed by basic researchers is an essential element of the total

research effort. And this principle, too, has several important dimensions:

-- Those engaged in the vital task of applications research must be in close touch with those who are doing the very best basic work.

-- We should, perhaps, seek new ways of supporting those who understand and can make interconnections between basic applications research in particular fields. These valuable individuals -- scientific impresarios if you will -- bring together -- for their mutual benefit, and for the benefit of all -- scientists engaged in different kinds of research who have the potential for creative interaction. The connection not just between basic and applied research, but also among research disciplines, is critical.

We must recognize, in short, the different types of scientific roles and provide support to those who are concerned about transmitting the learning of the laboratory to the society at large.

- Fourth, our government-supported research must have a strong orientation toward improving the quality of our nation's health and effectiveness of this nation's health services. Although we are spending ever greater amounts on health care in the United States -- more than $180 billion in fiscal 1979 or some 9 percent of the nation's Gross National Product -- there is substantial question whether billions of dollars of those expenditures have had any impact whatsoever on the health of the American people.

An improved knowledge base is vital to the central problem of health care in this country: providing quality health care at a reasonable cost. Indeed, as the vaccines so dramatically demonstrate, breakthroughs in research are often the means by which we can simultaneously improve health and cut the costs associated with disease.

Giving vitality to this principle involves applied research that, in candor, has not yet received its share of attention from the Old, Young, or Young, Young Turks. Some say that you have grown accustomed to treating applied problems, especially those affecting health delivery, like orphans, dumping them on the doorsteps of the schools of Public Health.

You can no longer abandon your responsibility in this area. You must work with the schools of Public Health as full partners. We need the best of the talents that the medical schools and the schools of Public Health can bring to bear. And we must remember that medical schools outnumber schools of Public Health by more than 4 to 1.

This fourth principle raises fundamental issues of health science.

-- The principle may involve new attention to basic problems: Problems like nutrition, or the aging of the population, or new methods of fetal research, or dealing with the bewildering set of questions surrounding detection and prevention, not simply cure, of environmental cancers. For example, this year we have requested an additional $33 million -- a 20 percent increase -- for the National Institute of Child Health and Human Development to seek new, safe, and universally acceptable methods of family planning, to

explore methods of producing healthy babies by correcting fetal deficiencies and to examine behavioral issues relating to birth problems in teen and sub-teen mothers who smoke.

-- The fourth principle may involve new attention to some of the disciplines I mentioned before -- disciplines like epidemiology and biostatistics; and behavioral studies that have important implications for national health problems. For example, I have asked that we undertake more research into the critical behavioral question of why people begin to smoke and what is an effective method of helping them stop if they want to do so.

-- The principle may also involve addressing some of the most basic issues: What is good health? How much health care is enough? How do we measure the quality of health care?

- A fifth and final principle is that HEW-supported research must be more effectively oriented to develop knowledge bases that support not just some but all the health missions of the Department -- prevention, delivery, regulation, standard-setting, and cost control.

It is now time to take a look at the health research strategy for the Department as a whole. We should reexamine whether our research resources are properly distributed among our health components -- the National Institutes of Health, the Health Care Financing Administration, the Food and Drug Administration, the Alcohol, Drug Abuse, and Mental Health Administration and other components of the Public Health Service.

Should there be greater research capacity within the operating components of the Department in order to increase the feedback between researcher and operator? Should there be a different set of questions addressed by researchers in order to help carry out pressing health missions -- such as reducing dangers from environmental causes, or discouraging and preventing excessive alcohol consumption?

As I noted, these principles are tentative examples of the formulations that we should develop this year as a prelude to the drafting of a more comprehensive five-year research plan.

I recognize, of course, that there is an inherent tension in the effort to produce such a plan -- a tension illuminated by the contrast between the first three principles I mentioned, which are statements in support of research without any indication of the directions in which that research might go, and the last two principles, which involve a substantive orientation of our research effort.

But it is our fate to live in an era of limited resources. Our society must learn how to make difficult choices wisely, and with foresight. We must shape a process in which the inevitable tensions I have highlighted will be creative -- a process that will produce a strengthened research enterprise which pursues knowledge openly and freely, for its own sake of course, but also to serve the health needs of the American people.

Thank you.

TECH

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

: Members
NIH Advisory Councils

DATE: May 15, 1978

OM : Director, NIH

BJECT : Secretary Califano's Initiative--Development of Health Research Planning Principles

In a recent speech before the Annual Meeting of the American Federation for Clinical Research, Secretary Califano announced that a national conference will be held at the NIH this summer to seek public advice in the development of health research planning principles for DHEW. The successful conclusion of this activity will lead to the development of a five-year health research plan based upon the principles established. Your participation in this process is essential for the NIH and the DHEW in developing a document responsive to the Secretary's initiative.

Attached are three documents, as follows:

- Attachment #1--Remarks of Secretary Joseph A. Califano, Jr., DHEW, before the Annual Meeting of the American Federation for Clinical Research, San Francisco, California, April 29, 1978.

- Attachment #2--Proposal outlining the process under which the DHEW health research planning principles would be developed.

- Attachment #3--Draft statement of the NIH health research planning principles.

Each Agency within the DHEW which engages in health research is involved in this initiative and will establish its own process to develop health research planning principles. Agencies' statements of principles will be consolidated for presentation to a national conference for review and recommendations to the Secretary. I believe that it is important to obtain your input as early as possible in this DHEW effort so that the NIH statement reflects the views of as broad a health community as is possible, given the timing of this initiative.

Towards that end, I would appreciate your review of the attachments, and your ideas and views on how attachments 2 and 3 might be improved and amplified for presentation to the national conference. I realize the difficulty involved in responding in a considered manner to documents which you do not have sufficient time to review. However, as

you can see from attachment #2, the timing of this process is extremely constrained. I encourage you to send written ideas to your Council's Institute Director. If your ideas could be received within a week, or at the most two, following completion of your Council meeting, they would be extremely useful to me in formulating an NIH statement.

Donald S. Fredrickson, M.D.

Attachments

cc:
B/I/D Directors
OD Staff
B/I/D Planning Officers
PPE Directors
Mr. Habel
Ms. Braymer
Mr. Mansfield
Mr. Miller

F
G
H
J

DRAFT
5/16/78

ATTACHMENT #2

Proposal: Process Under which the DHEW Health Research Planning Principles Should be Developed

Both the process and timing of this effort will be subject to DHEW review and possible adjustments; however, the NIH recommends that the following major steps be undertaken:

- Development of proposed health research planning principles by each agency engaging in health research activities (tentative completion date: early to mid July).

  Building on staff work already underway in each agency, this step should include:

  1. Reconsideration by each agency of draft documents previously developed suggesting health research planning principles for DHEW; and

  2. Consideration of each agency's draft health research planning principles by their respective advisory bodies where appropriate. Although each agency would not be required to solicit such advice, they should be encouraged to do so as a

means for obtaining broad public input prior to a national conference. NIH documents will be reviewed by the Institutes' and the Director's Advisory Councils, as well as by other outside advisors.

- Consolidation of agencies' proposed health research planning principles (tentative completion date: mid to late August).

This step should include the development of a unified document suggesting health research planning principles for DHEW which reflects each agency's input, consolidating where appropriate and identifying alternatives where consensus is not achieved.

- Presentation of proposed DHEW health research planning principles to a national conference (tentative completion date: late September 1978).

This step should include:

1. Determination of conference logistics and structure;

2. Endorsement or modification of health research planning principles where agency agreement exists and recommendations on alternatives; and

3. Collaboration between the DHEW and other organizations in developing the conference's structure and outcome.

o Development and publication of conference's outcome (tentative completion date: draft--late October or early November; final--early 1979).

This step should include:

1. Development of the conference's outcome into a document for presentation to the Secretary and acceptable for publication in draft as an approach to soliciting additional public comment; and

2. Development and publication of a final document, modified as appropriate based upon public comments received.

The completion of this effort will provide the basis for the subsequent development of a DHEW five-year health research plan. Consideration of the process under which the five-year plan should be developed need not wait until final publication of the health research planning principles, but might well be addressed immediately after the national conference. The development of the plan should provide full opportunity for public input.

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5/17/78

ATTACHMENT #3

Draft Statement of NIH Health Research Planning Principles

Background

The following points concerning the scope of the DHEW health mission are intended to provide a context for the development of health research planning principles:

- The principal health missions of the Department may be characterized as Health Research, Prevention, Health Care, and Regulation. Total Department expenditures for these missions in FY 1977 approximated $38.0 billion.

- In FY 1977, the Department paid 23% of the Nation's health bill; however, if the Health Care Financing Administration's (HCFA) budget is excluded, about 50% of the Department's health expenditures was for research and development activities.

- There are four principal health research agencies in the Department (NIH, ADAMHA, NCHS, and NCHSR)*; however, other agencies (FDA, CDC, HSA, HRA, HCFA)* carry out health research in support of their primary missions. Total expenditures for health research and development in FY 1977 by all Department agencies engaged in health research were $2.6 billion; expenditures of the four principal health research agencies amounted to approximately $2.5 billion (96%).

- In FY 1977, NIH and ADAMHA accounted for 92% of all Departmental expenditures for health research and development and for 97% of the health research and development of the four principal health research agencies.

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* NIH--National Institutes of Health
ADAMHA--Alcohol, Drug Abuse and Mental Health Administration
NCHS--National Center for Health Statistics
NCHSR--National Center for Health Services Research
FDA--Food and Drug Administration
CDC--Center for Disease Control
HSA--Health Services Administration
HRA--Health Resources Administration

- In FY 1977, the NIH expenditures for health research amounted to approximately $2.2 billion. Of this amount, about 76% of the NIH expenditures support Science Base activities, 14% support Clinical Applications, 5% support Transfer activities, and 5% support Training. NIH has adopted these new categories to provide a more functional way of viewing NIH activities and to indicate where these activities lie on the health research spectrum. Although not without definitional problems, these new categories briefly are conceived as follows:

  1. Science Base (S)--the search for new knowledge about fundamental processes of biology and behavior. This category encompasses both undifferentiated research which tends to be focused on underlying disease mechanisms and clinically oriented research which focuses on specific disease oriented problems.

  2. Clinical Applications (A)--the further development and assessment of knowledge for immediate practical purposes. Clinical trials comprise the largest element in this category, which also includes research on the development of vaccines, other biologics, drugs, instruments and devices.

3. Transfer (T)--includes demonstration, control, education, consensus development and dissemination activities, as facets of the total transfer of knowledge to the health care community.

4. Training (T)--the training of research manpower.

Introduction

In developing health research planning principles for the DHEW, it is important to recognize the following conceptual problems and constraints:

- Initially, the objective is to develop health research planning principles for the Department, not to develop a plan. However, the principles must be sufficiently specific to provide a context and framework for the subsequent development of a five-year health research plan.

- The principles must address all health research conducted and supported by the Department (including biomedical and behavioral research, health services research, epidemiologic and demographic research, research on disease control technologies, and health research communications), and must relate health research to the broader health missions of the Department.

- The principles must reflect the fact that resources for health research are limited. The planning principles are intended to serve as a structure for the subsequent development of a strategy to guide the allocation of Federal research dollars and to influence the manner in which the Department is organized to carry out its health research missions.

Health Research Planning Principles

The following set of principles are draft NIH proposals and do not necessarily reflect the views of other organizations that will be participating in this process. These principles are not mutually exclusive, nor are specific issues necessarily confined to a single principle. Rather, they are intended to complement one another, and it is through this complementarity that the unity necessary for Department-wide health research planning may be achieved. The principles proposed by NIH are as follows:

- Principle #1--The goals of improving the quality of health care, preventing disease, protecting health through regulation, and reducing the burden of health care costs are critically dependent upon advances in health research. The following key elements must be provided to assure unity of purpose:

-- Setting a realistically high level of Federal investment in health research. Over the past decade, total health costs have escalated from 39 to 120 billion dollars annually, while the proportion of health dollars devoted to research declined from 4.8% to 3.9%. The knowledge base to support Departmental health missions falls far short of needs despite extraordinary recent advances. Many research opportunities exist in areas of immediate and necessary interest, yet NIH and ADAMHA are able to fund less than 50% of the grant proposals recommended to them as meriting support.

-- Assuring the development of an adequate knowledge base for all Departmental health missions. This would include strengthening all research approaches to health problems--biomedical, behavioral, epidemiologic and demographic research, development of disease control technologies and research to improve biomedical communications--as well as finding more systematic ways of meeting the knowledge needs of the non-research health agencies. There is currently no systematic approach available to identify the knowledge needs of the non-research mission agencies, to make these needs known to the principal health research agencies, and to determine feasible ways of meeting these needs. Some questions to be considered here are what is and what should be the role of the health research agencies in establishing standards for health care, in providing the science base for regulatory efforts and in validating current

health practice. Another question is the extent to which health agencies with non-research missions should engage in application research in support of their mission and/or enter into arrangements with the principal health research agencies to obtain it.

-- Assuring the systematic dissemination of research results and related consensus development processes so that knowledge advances are applied to societal needs as promptly and effectively as possible. This will require research agencies to review new research information systematically, to identify clinically relevant portions needing further evaluation, and to assure an assessment of broader health significance.

o Principle #2--The DHEW should adopt a broad strategy for health research funding which includes:

-- Providing for an adequate level of assured long-term support for fundamental studies that expand the knowledge or science base for all Department health missions. This should be expressed as a constant dollar level for a five year period in order to assure continuity and effectiveness of ongoing research; current funding would serve as the baseline. New support levels should be related to an assessment of ongoing research, new scientific opportunities, and periodic evaluations.

This support should be recognized as a long-term investment which provides for freedom to pursue research topics that may not be immediately relevant to practical health problems and for diversity in the research supported.

-- Providing for specific program add-ons for the support of clinical applications research and transfer activities. This should include the funding of multi-year, high cost clinical trials and consensus development activities as direct add-ons to specific agency budgets together with the development of special funding arrangements for activities especially relevant to the mission needs of health care and regulatory agencies. These activities should undergo thorough review each year.

o Principle #3--Health research planning requires evaluation of performance and studies to illuminate future alternatives.

o Principle #4--Present research capabilities must be sustained to assure future health gains. These capabilities include:

-- Renewing and maintaining human and physical resources. It is essential to bring into the research community each year new investigators with new ideas and to provide them with research opportunities. This is necessary to train the next generation of investigators. Research careers must be kept

competitive with other pursuits in order to attract and retain high quality individuals. Serious attention must also be given to the Nation's physical research plant, which has been deteriorating. This includes funds for both equipment and facilities.

-- Fostering major research activity at research and academic institutions, such as medical schools, and providing research support in a stable manner. Research is inseparable from the learning process, and directly and indirectly enriches the quality of health care. Investigators and institutions should not be subject to major fluctuations in Federal policy and need some measure of stability.

-- Protecting the support of investigator-initiated research. Investigator-initiated research underpins the health research network, provides a large measure of stability to the system, and plays a critical role as a creative force in knowledge development and expansion.

o Principle #5--A prerequisite for research support is research opportunity:

-- That in the judgment of those best informed, the knowledge base in a given field will support further exploration, and scientific leads for new studies are available.

-- That scientific excellence and program relevance, as judged by those most knowledgeable within the research community, must remain the primary criteria for research support.

-- That, given research opportunity in fields where social costs may be estimated, research plans must weigh these costs. These should not only include direct care costs, but also morbidity, mortality and impact on the quality of life.

-- That emphasis will be given to prevention research where opportunities exist, because prevention is less costly and more effective than treatment.

o Principle #6--Efficient and effective discharge of the Department's health responsibilities requires complementarity of individual agency missions. This principle rests on the following key elements:

-- Assuring that the Department's organizational structure is responsive to all aspects of the overall health mission, and that each aspect is being considered in the most appropriate organizational locus.

-- Assuring the development of collaborative approaches to address those aspects of the health mission which cannot be

fulfilled by a single agency, or which are not exclusively contained in the mission of any one agency.

- Principle #7--The health research process must be sensitive to the larger social context in which it operates, thus:

  -- Attention must be given to ethical issues and social concerns. These include the protection of human subjects who participate in research, public safety and environmental health, appropriate representation of minority groups and women in research, and privacy.

  -- International coordination of health research must be strengthened. Because health research yields benefits to all mankind, it is essential to foster international cooperation.

PENDING HEALTH SERVICES RESEARCH LEGISLATION

Two bills, H.R. 12584 in the House and S. 2466 in the Senate, are now pending to authorize PHS programs for health services research, health statistics, and medical technology transfer and evaluation. Both bills were reported out of their respective committees on May 15 and await floor action. Authorizations for existing programs in these areas expire September 30, 1978.

S. 2466

The Senate bill would expand, redirect, and rename the National Center for Health Statistics and the National Center for Health Services Research, create a new National Center for Evaluation of Medical Technologies, and place these three entities within a new PHS agency to be called the National Institutes of Health Care Research (NIHCR). The NIHCR, whose Director would be appointed by the President, would be parallel to and modeled upon the NIH and would provide policy guidance and coordination to its component institutions in their conduct and support of health services research, demonstration evaluations, and statistical and epidemiological activities for the DHEW. Training programs in these areas would be authorized under the National Research Services Award authorities.

Briefly, the NIHCR would be composed of:

- The National Center for Evaluation of Medical Technologies (NCEMT) which would be responsible for assessing the usefulness, cost, safety, effectiveness, and the economic, social, and ethical impact of medical practices and procedures. It would be advised by a National Council for the Evaluation of Medical Technologies. The Center would be authorized to fund studies and train personnel in health practice evaluations. It would also be authorized to establish three extramural centers for the evaluation of medical technologies.

- The National Institute for Health Statistics and Epidemiology (NIHSE) which would incorporate the mission of the present National Center for Health Statistics and, in addition, would be directed to (a) coordinate all health data collection for DHEW and (b) undertake an expanded program in epidemiological research and research on improved methods of obtaining epidemiological data.

- The National Institute for Health Policy Research (NIHPR) which would incorporate and expand the programs of the current National Center for Health Services Research and which would be authorized to conduct policy assessments as well as research activities. It would also be given responsibility for reserach in the use of computer science in health services delivery and medical information systems.

AUTHORIZATIONS (in millions)

	1979	1980	1981
NCEMT	$25	$35	$50
NIHSE	60	65	70
NIHPR	40	45	50

H.R. 12584

The House bill would establish a National Center of Health Care Technology and otherwise retain existing organizational entities in the PHS. The bill revises and extends the authorities of the National Center for Health Statistics (NCHS) and the National Center for Health Services Research (NCHSR) and includes an explicit mandate for them to conduct studies relating to health care costs, including costs of diseases and conditions which are environmentally related. It also requires the establishment of: (1) a standardized means for collection of health information and statistics and (2) guidelines for collection, compilation, analysis, publication, and distribution of statistics and information necessary for determining environmental effects on public health.

The bill creates a new National Center for Health Care Technology (NCHCT) within the office of the Assistant Secretary for Health to support comprehensive assessments of the safety, efficacy, cost effectiveness, and the social, ethical, and economic impacts of new medical technologies. The NCHCT would be advised by a Health Care Technology Advisory Committee with NIH membership. The Center would be authorized to assist in the establishment of health care technology centers.

AUTHORIZATIONS (in millions)

	1979	1980	1981
NCHS	$60	$75	$80
NCHSR	36	44	49
NCHCT	15	25	35

THE NIH FORWARD PLAN

SECTION ONE. DIRECTOR'S PREFACE

DIRECTOR'S PREFACE

The NIH is the principal biomedical research agency of the Federal government. The objective of biomedical research, and thus of NIH, is to improve the well-being of man through greater understanding of life. This involves a continuing search for knowledge. This search is deeply rooted in biology and involves the successive resynthesis of new facts with what was earlier established, the entire process moving towards clinical application and the transfer of results to the health care community.

This plan, and the process which guided its development, represent an effort to describe this sequence and to address some of the significant issues which impinge on it. For FY 1979, the budget request and research plans show a shift in emphasis towards the expansion of "basic" research in NIH programs. This responds to a high administration priority for "basic" research in all Federal science programs, and a continuing NIH commitment to the development of fundamental knowledge needed for future clinical application and transfer to the health care community. In FY 1980-1982, the NIH commitment to "basic" research activities will continue. To exploit the output of this research, a substantially greater emphasis is planned for "clinical application" and "transfer" activities.

A New Approach

In past years, the terms "basic," and "applied" research have been used primarily for broad descriptive purposes. But they are troublesome when used as a basis for priority setting or resource allocations because they lack operational definitions and mean different things to different people at different times. Research is essentially an effort to gain new knowledge or to find a new way to use prior knowledge. Many scientists regard their efforts as "basic" no matter what the immediate purpose for seeking such knowledge may be. At the other extreme it can be argued that all research supported by the NIH is "applied," since its ultimate purpose is to apply the tools of many disciplines to biology to the ends of bettering human health. "Basic" and "applied" research represent the ends of the research continuum, and although it may be possible to identify activities at each end on which some agreement on definition can be achieved, there is an extremely large area of research in between which resists agreement.

In the past year, interest in the allocable implications of these terms has intensified, culminating in the administration's emphasis on "basic" research for FY 1979. At the same time, NIH has been engaged in an effort to redefine the research continuum and clarify the issues. The SATT approach--Science base, clinical Application, Transfer, and Training--is the first order approach. The NIH is attempting to use these concepts in its program planning and budget development activities. In using this approach, there still will be areas subject to

judgment; however, the definitions will be easier to apply, and the picture drawn of the NIH research programs will be more functional and reflect more accurately where the research activities lie on the continuum.

The new categories are conceived as follows:

- Science Base (S)--the search for new knowledge about fundamental processes. The terms of reference are scientific inquiry into fundamental matters of biology and behavior. Activities encompassed under this concept would include grant support for investigator-initiated projects, the larger, multidisciplinary efforts (known as program projects), some center-based activities, some intramural research efforts, some research contracts, and the provision of special resources for research. The science base includes both undifferentiated research which tends to be isolated from a specific disease orientation and clinically oriented research, focusing more on specific disease processes. The clinically oriented fraction, which is clearly part of the science base shades into another part of the continuum which is more rigidly defined as--

- Clinical Application (A)--the further development and assessment of knowledge for immediate practical purposes. Clinical trials, comprising the largest element in this category, are defined as a prospective research activity undertaken to assess the value and effect of prophylactic, diagnostic, or therapeutic agents, devices, regimens, procedures, etc., in human subjects. All NIH supported and conducted clinical trials are tracked and reported annually in an NIH clinical trials inventory. Other activities included under "clinical application" are research on the development of vaccines, other biologics, drugs, instruments, and devices. The outcome of these activities results in knowledge more immediately applicable to man and which may enhance the quality or duration of life. This knowledge, which will likely determine more codified medical practice, moves into the last part of the research continuum defined as--

- Transfer (T)--includes demonstration, control, education, consensus building and dissemination activities, as facets of the total transfer of knowledge to the health care community. Consensus building involves seeking agreement among informed members of the scientific community and the public on the probable usefulness of new clinical interventions, including an assessment of risks and benefits that may have been identified earlier through clinical research and/or clinical trials. Demonstration projects are time limited. They are undertaken to assure widespread understanding of the potential health impact of new applications--particularly those involving complex technology; and to provide the basis for their continued community support.

- Training (T)--training of research manpower. Critical to the above three categories is the continued training of new scientific researchers.

While the SATT approach recognizes both the flow of knowledge and its ultimate utility, definitional uncertainties and limits to its usefulness remain. During next year's planning process, the NIH will be trying to resolve some of the definitional problems, as well as considering the extent to which this approach can be applied usefully in the planning process.

Planning Agenda

There are currently three planning activities underway, all interrelated but running on somewhat different time schedules and addressing issues from different perspectives. These activities include:

NIH Planning Process

This process began in September 1977, and will be essentially completed with the publication of this document, the NIH Forward Plan, FY 1980-82. The major elements in this process have been:

- The provision of a forum for interaction and decision-making between the OD staff and the NIH Director with the NIH Institute Directors and their respective senior staff, as well as improved integration of the planning, financial and legislative functions. This interaction focuses on each Institute's program plans, opportunities for research progress, proposed allocation of resources, legislative proposals and major program issues. This process results in the refinement of the Institute's program plans, the development of a planning budget level, the initiation of action leading to resolution of or further work on program issues, and a mutually useful briefing in preparation for Congressional hearings.

- The identification of, planning for, and review of trans-NIH health problems. A number of health problems cut across the categorical lines of the Institutes and require a somewhat different planning effort. These health problems are reviewed within the same structure provided for the individual Institutes, and each Institute that has a program interest in the particular health problem participates in them. The review centers on the current status of planning for these health problems, including coordinating mechanisms in place, and the discussion of future activities.

- The integration of the budget and forward plan processes at all points throughout the eight-month planning period. This integration provides the NIH with a firmer planning base, a more realistic context in which to consider future program directions, and a more relevant structure around which decisions concerning research opportunities can be made. It also advances the NIH capability to develop the agency preliminary budget submission as a logical follow-through of the planning process.

- The review of Institute research programs within the context of the new SATT approach previously described. This approach provided a common framework within which activities and issues could be viewed as they occur in the sequence of knowledge development and provided a structure around which the general flow and direction of NIH activities could be assessed.

PHS Three-Year Planning Process

In February 1978, each Agency was asked by the Secretary, DHEW, to develop a three-year planning strategy. Individual Agency plans were integrated into a PHS three-year strategy document in the Office of the Assistant Secretary for Health. The NIH Research Strategy Plan, FY 1980-82 is reproduced in Section Two. This document was one outcome of the NIH planning process and the first attempt by NIH to describe its activities and allocate its resources using the new SATT approach.

DHEW Five-Year Research Planning

At the request of the Secretary, DHEW, the NIH is in the process of identifying major issues that the Department may wish to address in future long-range planning of health research and principals which could guide the development of such a plan. Each PHS Agency is currently engaged in a similar effort. The outcome of this activity will in large measure set the planning agenda for health research in the future. Some of the principals which NIH believes essential to the development of a long-term Departmental health research strategy are:

- Support for fundamental inquiry into biology and behavior--the "science base" for the Department's health missions--must be stable and at an adequate level;

- Assurance of funding in three areas is vital: support for free-ranging, investigator-initiated research; support each year for a number of new researchers with new ideas; and support adequate to train the next generation of investigators;

- Knowledge oriented institutions such as medical schools should continue to harbor major research activity, for it is inseparable from the learning process. Institutional concerns therefore must be taken into account;

- Excellence and relevance, as judged by those most knowledgeable within the research community, must remain the primary criteria for research support;

- A pre-requisite for research support is "research opportunity"--meaning that in the judgment of those most knowledgeable, the knowledge base in a given field will support further explorations, and scientific leads for new studies are available. Given "opportunity" in fields where social costs can be estimated, research plans must weigh not only direct care costs, but morbidity, mortality, and impact on the quality of life, as well;

- Because prevention is less costly and more effective than treatment, prevention research will be emphasized where feasible;

- Continuing provision must be made for storage, retrieval, and dissemination of the new knowledge derived from health research;

- There must be timely and effective transfer of new research knowledge for use in health practice, and to support the range of Departmental health missions;

- Annual budget and program reviews should focus on high interest, high visibility areas of clinical application and knowledge transfer, as well as on major new initiatives proposed. High cost clinical trials and consensus development should be funded--when feasible and needed--as direct add-ons to specific agency budgets.

Some of the issues that may be considered in the course of developing a five-year health research planning strategy for the Department could include:

- Science Base Issues

    1. How to sustain the capacity and effectiveness of the present national apparatus for health research;

    2. How to coordinate health research programs which transcend existing organizational structures;

    3. How to enhance, expand and evaluate research activities comprising the science base;

    4. How to more effectively serve the knowledge development needs of the regulatory and health care financing functions.

- Clinical Applications Issues

    1. What is the appropriate separation between health research and other health missions;

    2. What are the knowledge gaps which attend this separation and the options for closing them;

3. What is the appropriate role of health research agencies in validating existing health care practices; and

4. How can interface problems in multi-purpose disease-related centers be more effectively handled.

- Transfer Issues

1. What is the appropriate role of health research agencies in technology transfer;

2. To what extent is it appropriate for health research agencies to support "control" programs; and

3. How are technology transfer and assessment activities to be coordinated within the Department?

This Plan presents the NIH Research Strategy for FY 1980-1982 from an agency perspective, using the SATT approach as the planning framework, and the individual Institutes research program plans for the same time period. These efforts will contribute to the further delineation of major issues which will be addressed in the Department's five-year health research planning strategy.

D S Fredrickson

Donald S. Fredrickson, M.D.
Director
National Institutes of Health

brary of 36,000 displays. In the coronary artery system the displays are being revised constantly as new experience is gained. These revisions, made by the computer, provide directly authoritative information necessary to make decisions on subclassification (diagnosis), prognosis, and managment for individual patients. Computer simulation of clinical cognition has introduced an important "synthesis" concept. Here the final displays do not exist in a preformed set but must be built up by appropriate combination of small modules. The computer problem is to select and apply knowledge from its stores when it is required, thus freeing the programmer from the impossible task of prior specification of all possible contingencies. This concept of synthesis is also employed in INTERNIST which combines it with elements of probabilistic computations and pathophysiologic flow charts to build and select displays. INTERNIST keeps track of and displays both explained and unexplained findings. The hepatitis data base uses the computer for simplifying text editing and updating and for convenience of storage, retrieval, and dissemination.

In this brief review of examples of some of the classes of computer systems being developed to support diagnosis, prognosis, and therapy, there is evident a clear evolution of both an increasing sophistication of systems and a progressive recognition of the complexity of the problems. Also changing is the man-machine relationship. What may have been considered earlier as an adversary relationship is evolving through greater recognition and respect for the unique capabilities of each into a synergistic collaboration. Whatever the limitations of existing systems, the data justify an optimistic view of the future of this collaboration in medicine.

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The Road from Research to New Diagnosis and Therapy

Julius H. Comroe, Jr.

My career goal was teaching—not research. When I finished my internship, I became an instructor in pharmacology at the University of Pennsylvania because it was the best teaching department in the School of Medicine and I wanted to be part of it. (It was also the best research department, but that was a secondary factor in my decision.)

One learns a great deal by teaching, especially if one has bright, inquisitive, uninhibited students. The first thing that I learned (and I learned it the first day) was that I did not know the answer to many of their questions. The second thing I learned was that, for most of their questions, no one else had good answers either. In short, the areas of ignorance were far greater than instances of solid, real knowledge. That was in the mid-1930's. We could determine the specific type of pneumonia bugs in a patient, but we could not treat the patient because we had no sulfas or penicillin. We had x-rays that could detect shadows in lungs, but except for the vital capacity test, we had no tests of the function of the lungs. We had iron lungs (even built for two) for polio patients with respiratory paralysis, but we had no vaccine to prevent the disease in the first place. We could diagnose pulmonary tuberculosis, but we had no way to cure tuberculous patients because we had no streptomycin or para-aminosalicylic acid or isoniazid. We thought we were helping (or possibly curing) patients with tuberculosis by insisting on two plus years of bed rest in sanitoriums and by pneumothorax, but we know now that we really were not. We knew when a patient was not breathing and needed resuscitation, and the Red Cross had taught everyone in the country how to use the Schafer method of prone-pressure artificial respiration—until someone made actual measurements of the volume of "good air in" and "bad air out" and found it inadequate to sustain life; only then were adequate methods devised.

We could measure high blood pressure in the systemic circulation and diagnose hypertension there, but we could not measure pulmonary arterial blood pressure and diagnose pulmonary hypertension because Cournand and Richards had not yet done their basic studies of cardiac catheterization. We had no methods at all in the mid-1930's for resuscitation of the stopped heart and no artificial pacemaker to make a too-slow heart beat at a normal rate. We could tell, by looking, when newborn babies could not breathe properly and were blue, but we did not know why and most of them died; now research has shown us what causes the respiratory distress syndrome, and knowing that, we can treat it effectively and most of these babies now live.

My father, practicing internal medicine in the mid-1930's, had a few drugs (digitalis, insulin, arsphenamine, vaccines) that improved, cured, or prevented disease, and a few more (aspirin, morphine, barbital) that relieved symptoms of disease. Mainly he provided his patients with hope, encouragement, relief of suffering, and laxatives to keep their bowels open, and he recommended excision of foci of infection (mainly tonsils) and plenty of fruit juices (he had no faith in chicken soup). I, teaching in the mid-1930's, had few honest answers to

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Table 1. Steps between a new idea and full clinical application.

1. Man has an original idea or observation, or an important modification of a current concept
2. Knowledge must already exist or be developed in one or more related or unrelated sciences (for example, biology, physics, chemistry, mathematics, engineering, social sciences) that provides the scientific base, the concepts, the techniques or apparatus necessary to test the new idea
3. Man with idea (see step 1, above) learns of existence and pertinence of requisite knowledge (see step 2)
4. Man with idea now needs funds for experimental work to test his idea
5. Man obtains data, draws conclusions, writes manuscript, and submits it to journal for publication
6. Reader response to published article (does not read it; reads it but ignores it; reads it and repeats work)
7. Confirmation with or without modification and extension, or contradiction and refutation
8. New idea enters intellectual sphere of clinicians, of drug companies, of manufacturers of instruments or apparatus
9. Initial clinical trial (phase I) after approval of Committee on Ethics and Human Investigation
10. Application to Food and Drug Administration for phase II and III clinical trials
11. Publication of clinical papers; reports of successes and shortcomings
12. Approval by Food and Drug Administration for use by physicians
13. Widespread use of new drug (or procedure) by physicians
14. Further refinements of indications for use; cataloging of undesirable effects
15. Public acceptance of value of new therapy, which replaces no therapy or previous therapy
16. Continuing search for improved drugs or procedures

student questions except "I don't know." It was then that I realized what research was all about. Research meant that the teacher did not have to say "I don't know" year after year. Research meant that a physician did not have to say, year after year, "I can't cure you" to the vast majority of his patients. In short, research meant the end of a long static period in medicine—because every one of the great advances in modern medicine and surgery has come through research.

"Delivery of Health Care"

Why this long introduction that merely repeats what surely all of you already know? Because our attitudes and thinking are governed to a great extent in 1978 by catchy Madison Avenue phrases. One of these is "delivery of health care." What does this really mean? To me, delivery means distribution of something we already have, something that is stored either in a warehouse, a drugstore, a hospital, or even a physician's head. Those who prefer longer words would speak of it as delivery of the physician's present "armamentarium." A military analogy would be: if we have atomic bombs or nuclear missiles, we can both deliver them and at the same time try to improve the delivery system. But if we do not have them at all, the world's most perfect delivery system cannot endow us with the capability for nuclear attack.

So there are two ways to improve the nation's health: one is seeing to it that we deliver what we already have in hand, and do it fairly, evenly, promptly, intelligently, and guided by the best current medical judgment; the other is to find something better to deliver—earlier diagnosis, preventive measures, more effective treatment—and to recognize that these come through research and not through Madison Avenue slogans. We have become so enamored of the new phrase "delivery of health care" that we have already forgotten that we can deliver only what we have, only what we have already learned, and only what we now know. We forget that we will never have anything better or completely new to deliver—another disease to prevent, another disorder to cure—until we discover something new, and that is what we call research.

"Health Maintenance"

Another Madison Avenue catchphrase that needs some clarification is "health maintenance." My dictionary defines health as "physical and mental well-being; freedom from defect, pain or disease." It defines maintenance as "continuing or preserving a given condition." Health maintenance therefore must mean preserving in perfect health those who are now enjoying perfect physical and mental health. Because I know very few people to whom this applies on any given day or in any one year, this highly laudable objective, by dictionary definitions, probably applies to fewer than 10 percent of our population.

But, you may argue, the ills of the other 90 percent would be fully manageable if only the unhealthy would take the simple step of consulting a physician and following his advice to the letter. Not true. In 1978 our areas of ignorance about the human body and its malfunctions still greatly outnumber our areas of complete or sufficient knowledge, and the "health industry" (really the "sickness industry") has become the largest in the country. Unfortunately, experts testifying before congressional appropriations committees believe that the best strategy by which to obtain a larger budget for health or research is to tell anecdote after anecdote about the magnificent successes of medicine rather than to relate honestly how far we still have to go. Science writers are equally to blame for headlining daily "breakthroughs"; if one of them wants to win a Pulitzer prize in journalism, all he need do is follow up each "breakthrough" reported in the press and later write an article on the state of medical breakthroughs after 10 years. If I were looking for a research problem, I would do this myself.

I could list at length what we do not know: the cause of cancer, of hypertension, of atherosclerosis, of mental disorders, or of congenital heart disease; how to relieve low back pain, allergic disorders, arthritis, or even the common cold; how to transplant organs predictably and successfully; how to deal with major or even minor viral infections. A full list would use up too much expensive paper, and *Science* is already printing some pages with margins of only 1 to 2 millimeters. You can make a list for yourself of what we do not know by looking at your recently dead or dying friends and acquaintances, and the ones who wish they were dead, the ones with chronic disorders that will not let up and the ones who reply to your casual "How are you today?" with "so-so," or "not too bad," or "miserable." Or look through the Yellow Pages in your phone book and under social services and welfare organizations; you will find the words retarded citizens, alcoholism, cancer, blind, suicide, developmentally disabled, blind babies, epilepsy, emphysema, drug abuse, cerebral palsy, crippled children, deaf, mentally retarded, leukemia, multiple sclerosis, muscular dystrophy, visually handicapped, aging, heart, lung, and mental health. Obviously, Americans think there are a lot of medical problems still unsolved; why else would they be raising money each year to solve them? And even John Knowles, president of the Rockefeller Foundation and the staunchest advocate of the individual's responsibility for preventing disease, wrote in February of this year (*1*): "The support

of fundamental biomedical research has also flagged alarmingly in the past several years. The basic biological mechanisms of our most common diseases are still not well enough known to give clear direction to preventive measures."

If "health maintenance" does not refer to preserving the 10 percent in perfect health but rather to freezing our ailing population in whatever state of malfunction they now exist, and preventing its further progression, it probably involves 90 percent of our population. But it is then a phrase devoid of hope because it denies that we have the power to learn, to replace ignorance with knowledge, to cure the now incurable, to prevent the now "inevitable"—in short, it ignores the most important ingredient in achieving good health for most and then maintaining it, and that is research.

From Ignorance to Research to Application

Table 1 shows some of the steps along the road between the birth of a new idea or observation and its full clinical acceptance and proper use by physicians and patients. This is a compressed version of one road—a road for an idea that starts in a basic science laboratory, and eventually makes a fruitful connection with a clinical investigator. Omitted are the windings, the blind alleys, and the rocky and almost impassable parts. Rarely is the road shorter, because it is rare that someone takes one or two giant steps that eliminate the time-consuming problems.

Table 1 contains 16 steps. The first 7 involve basic or fundamental investigation which may or may not at that time be related to the clinical problem it is destined to solve. Steps 8 through 11 involve clinical investigation and often considerable participation by industry in research and development. Steps 13 through 16 include education of physicians, continued use of a new drug or procedure, refinement of its use, sharpening of its limitations, and acceptance of the new drug or procedure by patients who should be benefited by it.

Discovery: How to Promote It

Before discussing steps 8 through 15 in Table 1, I will summarize briefly data that Dripps and I obtained in an earlier study (2) of how the great clinical advances in cardiovascular-pulmonary medicine and surgery actually came about. Of 663 "key" investigations that were crucial to one of ten important clinical advances, 41.6 percent were not, at the time they were reported, related to that clinical advance, and 61.5 percent dealt with basic mechanisms of action of cells, tissues, or organs rather than with the diagnosis, prevention, or treatment of the disease itself. For each of the ten clinical advances, basic ideas, observations, or discoveries were essential either initially or later. Therefore to start a discussion of how to improve the nation's health at step 8 would leave a vital gap in understanding the processes of discovery and application and their interrelationships. To prevent this omission requires brief discussions of steps 1 through 7.

Although in our study (2), the crucial step was the first—the new idea, discovery, or observation—I know of no systematic, objective study by disinterested analysts on the selection, care, and feeding of those most likely to be innovative, creative, or inspirational scientists, the men or women who produce step 1. An old German recipe on how to make hasenpfeffer begins, "First you must catch the right rabbit." A modern recipe for promoting discovery would probably start, "First you must catch the right man or woman."

On the basis of my experience as director of a cardiovascular research institute for more than 16 years, I would enlarge the recipe to: "First identify individuals most likely to have completely original ideas, but give yourself 3 years to check on your judgment (that is, your talent in clairvoyancy). During this time, give your nominees facilities in which to work; provide an intellectual environment conducive to an exchange of ideas with scientists in many related and unrelated fields; shield them from nonproductive activities; relieve them from the time-consuming and nerve-wracking experiences of obtaining research support; and encourage them to develop and follow through new ideas regardless of the number or weight of their publications."

It takes experience to identify the right man or woman initially, self-restraint to let him make mistakes and go into and out of blind alleys, self-denial to create for him the freedom and intellectual environment that you would dearly love to have for yourself, and fortitude to say, after 3 years, "You're not going to be a step 1 man, but you're going to be a great step 7, 8, 9, 10, or 11 man."

What if he *is* likely to be a step 1 man? Is there any way of maintaining an ideal environment for him for all, or at least a considerable portion, of his scientific life? From the very beginning of the Rockefeller Institute for Medical Research (1901) and of the intramural laboratories of the National Institutes of Health, such an environment has existed for a limited number of scientists. It also exists for the career investigators of the American Heart Association, the lifetime research professors of the American Cancer Society, the lame-duck research career awardees of the National Institutes of Health, and for a small number of research professors supported by university endowments or private foundations or institutes. And recently some pharmaceutical companies have established the equivalent of research professorships in "pure research" laboratories.

I am often amazed that scientists, who insist on rigid scientific proof in their laboratories and in those of others, act on their "gut reactions" when it comes to answering questions such as how to foster discovery. It would be worthwhile to evaluate the contributions (their direct contributions and equally important indirect ones through training and inspiration of others) of American research professors (or their equivalent) since 1900 and come to a conclusion on the likely advantage to health of increasing the number of 5-year, 10-year, or lifetime research professors. I believe (gut reaction) that the advantage would be considerable, but I would like to have the facts.

Research-Research Interfaces

It was once possible to go directly from step 1 to step 13, with perhaps only a perfunctory stop at one or two intermediate steps. Withering, in discovering and using digitalis in 1785, needed little help from those in other branches of science because he himself was a botanist, clinician, mineralogist, and chemist. The interfaces in his discovery were between his own brain cells that stored information in botany, chemistry, and medicine, and these neural connections quickly enabled him to identify the foxglove as the only ingredient of a Shropshire potpourri that was likely to have potent biological activity; the century in which he lived allowed him to skip interactions with editorial boards, peer review committees, the committe on human rights, and the Food and Drug Administration.

It is rare today that one man can produce, store, recall, and relate all of the knowledge needed for a major advance in science. Let us consider the important development of open heart surgical pro-

cedures. In 1954, John Gibbon performed the first repair of a human heart while the needs of the patient's body were met by an artificial heart-lung apparatus. But many others, starting as far back as the 17th century, first had to make essential discoveries in a wide variety of fields (and Gibbon had to know and make use of these) before open heart surgery could become predictably successful (2). Obviously, Harvey first had to discover the circulation of the blood (1628) and Hales (1733) had to learn how to measure arterial blood pressure. For the success of ordinary blood transfusions, Landsteiner (1900) had to discover human blood groups; Hustin (1914) had to find that citrate was a satisfactory, nontoxic anticoagulant; and Rous and Turner (1916) had to learn how to preserve blood, a study that led to development of blood banks. Physiologists had to learn that a heart could be stopped and restarted ("for sure") on demand. Whole new sciences of anesthesiology, bacteriology, immunology, pharmacology, and chemotherapy had to be developed, and the principles and practice of asepsis and antisepsis had to be established and used.

Could better interdisciplinary services have brought together the knowledge required for open heart surgery 50 or 100 years earlier and permitted it in 1846, shortly after the discovery of surgical anesthesia? No, because critical, essential knowledge was unavailable until 1934. The critical factor was the need for an artificial heart-lung machine that could maintain blood flow throughout the body when the patient's own heart had to be stopped for a while to allow the surgeon to repair intricate structural defects. Some have noted that 1934 was the year in which DeBakey published the report on his roller perfusion pump. But perfunctory library research by someone who desperately needed a DeBakey-type pump earlier would have shown that details of it had been published in 1932 by Van Allen and even earlier, in 1928 (3), by Bayliss and Müller (who turned it over to Palmer Ltd. for manufacture) and that a man named Kelly had obtained U.S. Patent 314851 on it in 1885. The pump was obviously not a limiting factor.

A more likely critical factor was the absence of a nontoxic anticoagulant, and it is hardly accidental that Gibbon began his long research program on a heart-lung machine in 1934, the very year that heparin (a naturally occurring, nontoxic anticoagulant) became commercially available. However, the laboratory discovery of crude heparin came in 1916 and an earlier Gibbon might have forced its purification 10 to 15 years earlier than 1934. Maybe work on the heart-lung machine began in 1934 partly because the essential knowledge became available in that year, but it is more likely because Gibbon became available in that year. He had an idea and intense conviction that a pump-oxygenator could replace the natural heart and lungs for short periods; it turned out that he could not be dissuaded from his goal by the indifference, ridicule, or scoffing of his surgical colleagues. [It is important that goal-directed, mission-oriented science administrators know that Gibbon spent 13 years (1934 to 1947) trying to perfect the heart-lung machine, not for open heart surgery, but to allow time for a surgeon to remove an embolus blocking a patient's main pulmonary artery. It was only in 1947 or 1948, on the urging of Alfred Blalock (of blue-baby fame) that he switched his goal to providing an instrument that would permit repair of cardiac defects (4).]

Linkage Between Steps 2 and 3

Those who would like to accelerate research and its application to clinical medicine would do well to think long and seriously about establishing effective linkages between steps 2 and 3 in Table 1. One can list innumerable instances in which research in medicine was speeded by connecting knowledge in one or more of five or six biological or nonbiological sciences with a difficult problem in medicine. We are today drowning in scientific literature in all fields, and I think it is time we do something other than publish more and thicker journals, more and thicker books, more and thicker review articles. A new catchphrase is "promoting the *diffusion* of scientific knowledge." Lord help us if we can't do better than let it *diffuse*. As I have noted elsewhere (5), diffusion is an intermingling of molecules resulting from the random movement of each. It works rapidly over short distances such as micrometers, but takes forever over long distances. Can't we pinpoint where special new knowledge should go and get it there by special delivery? The ideal instance of special delivery was the daily interaction between brother Ernest (the physicist) and brother John (the physician) Lawrence that allowed radioactive isotopes to jump directly from the cyclotron in Berkeley to clinical investigation in Berkeley. Another special instance of interaction, regarded by the participants as very exciting moments in their scientific lives, was the lunchroom at the Rockefeller Institute for Medical Research, where great scientists in many disciplines learned daily from informal conversations with others. It is too much to arrange this in very many cases. Further, there are well-recorded instances of direct suggestions, given to biological scientists by others, that were ignored, although if they had been investigated, they would have accelerated important discoveries by decades. ("You can lead a horse to water but you can't make him drink.")

I do not have answers but I do have questions: Is there a way of preparing interdisciplinary reviews that will synthesize current knowledge, emphasize important areas of ignorance, and offer thoughtful suggestions on how to learn what we need to know? Can we do all this in simple English that any scientist in any discipline can understand, and make these special reviews easily available to all without the necessity of subscribing to 30 journals? Many physical or biological and chemical scientists do now engage in interaction, but at this very moment the Federated Societies are pulling apart with biochemists meeting separately from the other bioscientists; the annual reviews in all branches of biomedical science are becoming more and more highly specialized so that they become more difficult for an outsider to read. Even *Scientific American* is becoming more technical and more of a struggle for "outsiders" to read. Can this tendency to ultranarrow, microspecialization be slowed down or reversed?

The first business of the National Academy of Sciences is a legal requirement—to advise the government on scientific matters; should not its second business be to tell all scientists in all fields of important new advances in each and how these might have important implications for their fields? The National Academy of Sciences is an interdisciplinary group elected from 23 branches of science including anthropology, astronomy, botany, chemistry, engineering, geology, geophysics, physics, psychology, and the social, economic, and political sciences in addition to ten biological sciences. Would not its *Proceedings* serve all sciences better by bringing them together instead of acting as a huge rapid-publication journal for very narrow aspects of two or three of the currently popular biological sciences?

Funds for Research and Development

A new idea can help no one unless it can be tested. A new idea when tested and confirmed cannot help patients unless it is carried further and, if possible and appropriate, brought into the sphere of clinical investigation and practice. Nowadays, all of this—which we call research and development—requires large sums of money—from federal agencies, voluntary health agencies, privately funded foundations, and institutes and industry, to name the main sources of funds.

Let us consider here only the National Institutes of Health (NIH) and its support of basic research and clinical application. Let us assume for the sake of this discussion that Congress has decided to maintain the NIH budget at its present purchasing power—that is, at its present dollar level plus allowances for overall inflation (in salaries and usual research supplies), plus allowances for the soaring costs of hospitalization that increase the price of clinical investigation year by year, plus allowances for purchase, maintenance, and replacement of now-essential, highly sophisticated, and expensive research equipment that has replaced test tubes, sealing wax, and smoked drums in basic research laboratories.

Because federal allocations of "real" dollars for biomedical research cannot increase indefinitely (unless tied by formula to increases in the gross national product), a policy that stabilizes the purchasing power of NIH dollars over a long period should solve many problems.

But one problem that it will not solve is that something more is needed than stability in congressional appropriations; the something more is a science policy and statement of priorities. Why? Because there are many ways of using funds allocated by Congress to NIH and no rules for the use of these funds. Let me give a few examples.

1) Congress divides the total NIH budget into allocations for each of its Institutes. It may also earmark a portion of an appropriation to an Institute for a specific project (such as sickle-cell anemia) or set an upper limit to a specific type of ongoing program. These actions are in a sense a congressional statement of priorities, but none carries with it more than a 1-year commitment.

2) An Institute director may divide the nonearmarked or nonrestricted part of his annual budget into funds for contracts and funds for research grants. Contracts usually pay for development of apparatus, equipment, or special research materials (much of which industry once considered to be its obligation) but they may be used also to pay for clinical trials; research grants, for the most part, pay for research on ideas and programs initiated by individuals or by small groups of scientists.

3) The Institute director and his staff may further subdivide the funds allocated for research grants into those that support some large and expensive cooperative clinical trials (that clinicians in university hospitals once regarded as a normal obligation and responsibility) and those that support basic research on new ideas and their refinement. Policy on this subdivision is not necessarily consistent for the components of a single Institute and may change yearly or seasonally.

This decision-making power may work to the advantage of the scientist with a new idea (our step 1 man) or it may work against him; when Congress, the President, and the Office of Management and Budget are in a mission-oriented, "let's apply what we know" mood, it works against him.

4) Peer review of grant applications also presents a problem. A large group of nongovernmental scientist-consultants constitute regular peer review groups ("initial" review groups) that set priorities on the grant applications that are sent to them for evaluation. The regular peer review groups have received almost universal praise (in this country and abroad) and deservedly so. But not all applications for grants and none for contracts go to them for review. Those that do not are usually sent to ad hoc or standing "special" review groups. If the special review groups award higher priorities (better scores) than do regular peer review study sections that have different standards, the total review system can result in diminished support for the step 1 man with the new idea (6).

5) By law, the National Advisory Council to each Institute of NIH can change the priority score of the initial review group (peer review study section) so that a disapproved grant may be paid or an approved grant not paid, on the basis of the Council's scientific judgment or its assessment of "programmatic importance" to the Institute. In the absence of a national biomedical science policy, this can also diminish support for the step 1 man.

I have my own convictions on the support of research versus development; on support of undirected, basic, fundamental research versus applied, mission-oriented, goal-directed research. It is that all are important and essential and that their support should not be discussed as an either-or proposition. But a decision must be made on how much for this and how much for that, and in the interest of good, uninterrupted research, the policy decision should hold for a reasonably long term.

I believe that if we had a highly intelligent, rational, and logical visitor from a planet in outer space (say Mr. Spock of Star Trek fame, who cannot be emotional but only logical), he would give the highest priority to fattening the goose that lays the golden eggs rather than killing the goose in order to save the money required to feed her.

If I had a vote in establishing a national biomedical science policy, I would give my top priority to guaranteeing an adequate, irreducible, undivertible sum, in the form of long-term grants, for the step 1 men, and give national peer review groups the challenging responsibility for identifying step 1 men. How much is adequate is a matter for careful study and should not be an off-the-cuff decision. I would also vote that the Institute director and staff should have adequate funds to support (after peer review) research in important areas that, in their best judgment, has been neglected nationwide by the collective applications for regular research grants. And I would vote that someone would have responsibility for eliminating excessive duplication of research effort by the "me-too" researchers who drain away dollars badly needed for creative, original research.

Journal Review and Reader Response

There is not much of a problem today in getting a scientific article published. Often a scientist fails to have his article accepted by his first-choice journal, a prestigious one which also has the largest appropriate audience. Often he is maddened by orders from an editor to "cut it in half," or to eliminate speculation or suggestions for future research, or to remove what he considers essential illustrations, or by inordinate delays in publication after acceptance. But some journals have been innovative in shortening publication time, in publishing controversial articles that do not have unanimous acceptance of the editorial board (often with a cautionary editorial in the same issue), and in encouraging rather than prohibiting speculation.

Much greater problems are getting subscribers (i) to open their journals, (ii)

to read the table of contents, (iii) to read even a single abstract or summary, and (iv) to read an article itself. One journal has tested how far a reader goes into its journal by inserting a genuine $5 check in mid-journal, but I do not have the data on how many of these were discovered and cashed.

Riva-Rocci, who wrote in 1896 about his arm cuff for measuring systolic arterial blood pressure in man (7), apologized for not having read Rabinowitz's modification of von Basch's device until he (Riva-Rocci) had completed his work, and asked that his readers forgive him "on the score of the vastness and diffusion of the current literature on any given subject." Multiply that vastness by 1000 or 10,000 and you will see the most critical problem today in translation of results of research into clinical investigation and clinical practice, and the area in which investigators and physicians alike need most imaginative and effective help. I am convinced that scientists would learn more by speaking less, by participating in fewer symposia, by writing less, by traveling less—*if* they devoted time so saved to intensive reading of what others are doing; but reading is less glamorous and less ego-satisfying and not deductible from income taxes. (Earlier, I have given suggestions for helping the scientist learn of advances in a variety of sciences.)

From the Laboratory to the Clinic

Occasionally the same man produced or purified a new drug and was also the first to use it clinically (Florey and Chain, penicillin; Banting and Best, insulin; Withering, digitalis); no interaction or transfer from laboratory to clinic was involved. Occasionally a clinical investigator was constantly in the wings, fully prepared to test a promising new compound developed in a basic science laboratory (Feldman and Hinshaw were at work testing streptomycin in mice with experimentally produced tuberculosis within a month or two after publication of Waksman's first preliminary report on their new antibiotic agent). Very often the same man who constructed new equipment was also the first to use it clinically (Zoll, the defibrillator and cardiac pacemaker; Gibbon, the pump oxygenator; Drinker, the body respirator); again, no interaction or translation was involved.

I know of no complete study of how many clinically useful drugs (i) originated in nonprofit research laboratories and were then purified, put into proper form, and marketed by pharmaceutical companies, as opposed to drugs that (ii) originated in research laboratories of the pharmaceutical laboratories, were then tested by clinical investigators elsewhere, and were finally marketed by the company whose staff initially discovered, purified, or synthesized them. In our study of key advances necessary for modern treatment of cardiovascular-pulmonary diseases (2), we found that industry had a remarkably good record in supporting basic chemical and pharmacological studies that led to clinically important drugs; about half of 50 such drugs came entirely from the efforts of scientists in industry (for instance, oral diuretics, sulfanilamide, numerous antibiotics, propranolol). The drug industry has also had a good record in supporting basic research of not-for-profit groups, in supporting clinical investigations of new drugs, and in supplying nonprofit groups with countless modifications of a parent compound in the hope that one might be clinically useful.

Dealt with elsewhere in this issue are the ethical and moral considerations that a clinical investigator faces when he first uses a new drug in volunteers or patients, the requirements of the Food and Drug Administration that must be met before it approves a drug for use generally by physicians, and the necessary delays involved in compliance with these. The exemption from regulation of new surgical procedures, or modifications of old ones, is another matter that I will not discuss, although it is an important issue.

In our study, the record of manufacturers of equipment and apparatus was not an impressive one. Of 65 new types of equipment needed for advances in cardiovascular-pulmonary medicine and surgery, the basic principles, prototype, and early modifications came from university or other nonindustrial laboratories in 55 cases; only ten came from initial research and development in industries' own laboratories. Lags of at least several years occurred before private industry decided to produce items of equipment that had been generated in not-for-profit laboratories and make them widely available. On the other hand, when the president of a company took a personal interest in developing a new product (for instance, IBM's Watson and Gibbon's pump oxygenator), progress was rapid.

It appears that the nonpharmaceutical industries are not well prepared to judge the potential value of new biomedical instruments and apparatus or prefer not to become involved until satisfactory sales and profits are assured, or both. How to shorten delays caused by industry's caution is a complex problem which has been the subject of several studies.

Continuing Education of Physicians

Few medical students, interns, or residents receive formal training in critical evaluation of medical literature, yet they are expected to continue their own education for their professional lifetime. There is no dearth of medical journals that publish new scientific work in medicine and surgery and there is certainly no lack of attractive advertising designed to introduce to physicians the uses and advantages of new drugs and procedures. What physicians need more of is easy-to-read, short, authoritative articles giving the best medical judgment on the value and limitations of new scientific work. Medical magazines supported by advertising rather than by subscription fees were the first to recognize this need and fill it. Some of the more prestigious medical journals have recently begun to evaluate new reports critically and to publish side by side both aspects of controversial issues.

I believe that periodic reaccreditation of practicing physicians presents the best hope of solving the "keeping-up-to-date" problem. It is obviously going to create a huge new industry. If it does its job well, it will have some advantages over journal scanning. First, continuing education will challenge existing teachers in universities and the new industry that deals with learning techniques to devise ways of presenting medical science clearly and succinctly to busy practitioners. Second, in many instances, it will bring the faculty and "students" into direct contact and so permit immediate clarification of difficult presentations. Third, it will bring unusual clinical problems of practicing physicians to the attention of faculty trained in clinical investigation and this can direct the attention of the latter to matters that merit serious investigation. (The burgeoning new industry of medical information systems is discussed elsewhere in this issue.)

Public Acceptance and Responsibility

Many of the public are or want to be well informed on medical matters, but few are prepared to cope with medical jargon or with completely contradictory opinions from two "highly authoritative" physicians or scientists. The jargon problem can be solved only by editors

with supersensitive jargon-detectors and complete authority to eliminate jargon and gobbledegook from all written or spoken material directed to the lay public. The problem of controversy and what to do when authorities disagree must be presented squarely to the public, and the public must learn that medical scientists believe that certain things are currently "for sure," that they are presently in disagreement on others, and that they have at the moment little secure knowledge on still others.

The public also deserves to be told the difference between factors that directly and with certainty cause (or prevent) disease, and risk factors that do not cause disease with certainty but do increase the risk that a disease will occur or become more severe. Then the public also deserves to be fully informed about causative factors and risk factors and (i) what the chances are (such as 9 in 10, 1 in 10, 1 in 1000, 1 in 1,000,000) that continuing to take the risk will result in earlier death or disability, and (ii) what the chances are that following a prescribed program will prevent disease, prolong life, and improve the quality of life.

The statement has often been made that more than 20 million people in this country have hypertension, that half of these do not know they have it, and that half of those who know they have it are inadequately treated, often because patients elect to discontinue treatment. Because hypertension by itself may produce no symptoms if mild and of recent origin, but increases the risk that the individual will acquire coronary artery disease or stroke, the National Heart and Lung Institute has conducted a Hypertension Information and Education program for several years. Its goal is to identify the 10 million individuals who are believed to have hypertension but do not know it, and to inform all of the 20 million with hypertension of the availability of drug treatment.

Considerable criticism has been directed against the public for not seeking diagnosis or, once a diagnosis has been made, for not following a recommended drug or dietary regime. It appears that we are approaching a national debate over compulsory diagnosis, treatment, and prevention of noncommunicable diseases (to eliminate hospital costs and unemployment caused by preventable or treatable illness) versus the right of an individual to know the risk factors involved and then be free to decide whether he prefers the treatment to the risk in no treatment. The historical point of view teaches us that much of what we once knew "for sure" was later disproved and suggests that some of what we now know "for sure" will one day be proved wrong (such as, regular exercise prolongs life, cancer of the bowel is caused by the food we put in it). It also suggests that in the long run a well-educated, well-informed citizenry will more often than not make the right decison. With physician education and public education going hand in hand, issues such as that discussed above may well be solved without first repeating the mistake of the prohibition amendment (which made one medical risk factor illegal but still available at a price).

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4. Mrs. John Gibbon, personal communication.
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6. A 12-member team, headed by R. Kirschstein, recently carried out a comprehensive evaluation of the peer review system for evaluating NIH research grant applications. It was completed in January 1977, and on 8 February 1978 the NIH director issued his decisions based on the Kirschstein report. He approved 42 of their recommendations. Among these were: "Special efforts must be made by reviewers and staff to identify unique or unorthodox research. The need to be alert to unique ideas should be stressed in the orientation of new members of initial review groups and councils and in the Guide for new members. . . . The responsible officials and staffs of the various initial review groups or Advisory Councils/Boards [shall] hold annual orientation sessions for their new members in order to place peer review in perspective and to inform reviewers of their functions, duties and responsibilities. . . . The peer review system must remain alert to innovation. . . . Training curricula [shall] be developed by NIH for extramural program and review staff in order to provide orientation and to refresh and reiterate principles concerning the philosophy, objectives, and procedures for peer review. . . . *Initial Review* Groups [shall] be requested to identify applications they consider to be especially creative or innovative."
7. S. Riva-Rocci, *Gazz. Med. Ital. Torino* **47**, 981 (1896); *ibid.*, p. 1001.

Surgical Innovation and Its Evaluation

J. P. Bunker, D. Hinkley, W. V. McDermott

Many observers have called attention to the inconsistency of controls and regulations governing the introduction of new therapies in the United States (*1*, *2*). New drugs are introduced in a manner conforming to strict federal regulations that require rigorous testing in animals according to careful experimental designs, followed by carefully controlled testing in humans with appropriate protocols and follow-up observation. In contrast, new surgical operations may or may not be tested in animals, may be introduced as human therapy with or without review by a human experimentation committee and with or without a formal experimental design, and may or may not be evaluated by long-term follow-up observation.

The question is asked: Why should operations not be subjected to testing and controls that are as timely and no less rigorous than those required for drugs? In an effort to answer this question, and to suggest solutions for problems found, we have reviewed the process by which four relatively new operations were introduced and evaluated. Three of the four were subjected to randomized clinical trials (RCT's), but only after the passage of much time and many procedures, and it was apparent that earlier trials would have speeded the process of evaluation in each case. Shortcomings in the evaluation process also included lack of systematic and comprehensive collection and reporting of clinical experience. Early clinical surveillance could have facilitated the design and early implementation of RCT's when necessary. Of

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PETER BARTON HUTT

Public Criticism of Health Science Policy

Public criticism of science and consequent attempts by the government to impose control over scientific inquiry are not recent phenomena. It is doubtful that scientific inquiry has ever been truly unfettered, or that any responsible scientist would argue for such anarchy.

It is likely, indeed, that scientists today enjoy greater freedom of inquiry than ever before in history, in terms of both public support through use of tax funds and reasonableness of government restriction.

Public criticism of current health science policy has not sprung full-blown upon an unsuspecting scientific enterprise. It began years ago, and has steadily increased in intensity. Perhaps because of its extraordinary success in attracting sustained congressional support for health science research during the past few decades, the scientific community has paid little attention to this growing criticism. Even when given the opportunity or mandate to analyze and rebut this criticism—for example, when Congress established the President's Biomedical Research Panel to review and assess national biomedical and behavioral research conducted and supported under federal funds—the scientific community has not dealt with it directly, and in some instances has ignored it completely.

Some of the criticism amounts, of course, to little more than rhetoric and hyperbole. Scoffing at even this type of criticism, without patient and objective analysis and a mustering of all available information to refute it, is a very dangerous mistake. Even the most absurd accusations, when repeated time and again without refutation, can gather a following and momentum that defy common sense.

Lawyers are trained to pay little or no attention to those who agree with them, and instead to concentrate on answering the arguments of their adversaries. The scientific community has regrettably given the impression that there are in fact no convincing answers to be given, because it has failed to meet the criticism of current health science policy head on, to debate it publicly, to concede those points where criticism is valid, to present a sound rebuttal where criticism is demonstrably unwarranted, to admit where further inquiry and information are needed to determine the validity of criticism and then to set up methods of gathering the needed information, and to pursue these issues in every public forum available.

In the scientific arena, the scientist is accustomed to setting up hypotheses, testing them with experimentation, declining to offer conjecture until adequate

data are available to support or refute the hypotheses, and even then limiting his observations to those things that are objectively proved and waiting for new hypotheses and investigations before again venturing to suggest additional conclusions. In the public policy arena, in contrast, he is reluctant to engage in any disputation and indeed feels extremely uncomfortable about participating in any debate at all, he remains silent or relies upon conjecture and appeal to emotions rather than attempts at objective analysis, and he is affronted and bewildered when an uncomprehending public rejects what he believes to be self-evident propositions of sound science policy.

Scientists, if they are to be credible and, more important, if they are to be effective in maintaining the extraordinary level of freedom of scientific inquiry that exists today, must begin to apply more rigorously in the public policy arena the same principles of investigation and proof that have worked so well in the field of science itself. The scientific community cannot afford to permit criticism to continue unrebutted until it is accepted by the general public as undisputed statements of fact.

The first step in the process of rebuttal is to catalog the public criticism of health science policy in this country so that it can be analyzed and subjected to proof or refutation. The remainder of this paper constitutes an attempt simply to do this. The catalog is culled from a wide variety of sources, including hearings and reports of Congress, reports of government agencies, and speeches and position papers prepared by individual scientists and nonscientists and published or summarized in journals, magazines, and newspapers. It is not arranged in any order of priority, and is undoubtedly incomplete. However, it contains sufficient challenge to occupy the scientific community for some time to come.

Some of the criticism may seem totally unjustified and even purposely offensive. No attempt has been made either to embellish existing criticism or to tone it down; it is simply set forth in the terms in which it is often heard in public policy debate. Many of these issues are emotionally charged, and virtually all are advanced by supporters who believe fervently in the logic and righteousness of their position. The scientific community cannot afford to take offense regardless how it may resent the tone and innuendos, or even the nasty accusations, that some of this criticism entails.

Finally, it is important to emphasize that this catalog does not represent my own views or those of any other particular individual despite the direct declarative mood of the sentences in which it is written. It is intended to present a list of public criticism, not to debate the merits of the issues involved.

I. Health Science Research Is Not Presently Designed to Help the Public Which Pays for It

A. *Appropriations for health science research funds must be justified in terms of demonstrable and immediate public health benefits rather than in terms of vague promises and hopes that, in time, basic research will provide solutions to all health problems.* The public has been deluded too long with promises that all human disease can be prevented, controlled, or cured, if only more and more public funds are poured into health science research. Tax money is becoming scarcer and scarcer each year, and only those research projects that promise a tangible public benefit in the very near future should be regarded as worthy of federal funding.

B. *Little research is done to develop a national research policy attuned to public needs.* There have been only a very few published papers analyzing how health science research priorities should be established. Significant federal funding should be devoted to determining an appropriate strategy for setting such priorities, communicating them to the research community, encouraging research into important areas of national need, coordinating research on questions of major public significance, and assuring rapid technology transfer so that the public will receive maximum benefit.

C. *There is no attempt to set research priorities on the basis of the projected benefit to the public of reducing the public burden of illness.* The objective of federal funding of health science research should be to eliminate or alleviate the morbidity and mortality associated with those health problems that have the greatest impact on the public. The federal funding agencies should establish a method of pinpointing those health problems which impose the greatest burden on the public, determine the research priorities which have the greatest potential for affecting those problems, and then fund those research proposals which directly address those priorities. Scientists would remain free to pursue whatever other interests they may have using nonfederal funds, but scientific information that has no potential impact on public health is of little value to the public and should not be funded by federal agencies.

D. *The free enterprise market mechanism represents the best model for assuring that the right kind of health science research is undertaken.* It is in the best interests of private industry to determine where the greatest burden of illness falls on the public and to devote research expenditures to those areas, since they represent the greatest potential market and thus the greatest potential source for profit. This is the classic example of the free market working in the best interest of the public. Federal funding should either be subjected to the same principles or should be discontinued.

E. *Research priorities should not be determined by the interests of researchers.* Under present federal policy, research grants are awarded on the basis of research proposals submitted on the initiative of the individual researcher. Accordingly, it is the interests and priorities of researchers which largely control the nature of health science research undertaken through federal funding.

Those health science issues that are of primary importance to the nation, rather than those that are of primary interest to researchers, should receive targeted federal funding. Federal agencies should determine the most important health needs facing the country and then fund only those projects which are directed towards meeting those needs. Allowing researchers to follow their own interests is far less likely to bring results that truly reflect national health priorities.

F. *Research projects should not be directed to abstract and artificial issues that bear little or no relation to possible health benefits to the public.* Without doubt, there are many possible research topics that could be of intellectual and academic interest. But federal funds, which will be increasingly scarce in the future, should be used to support only those health science research projects that have the greatest potential for improving the public health.

G. *Research priorities should not be allowed to be influenced by the need a researcher feels to pursue the "latest" issues in order to keep up with his peers.* It is true that every individual is subject to peer group pressure, and that everyone wants to feel

that he is part of the most interesting new developments in his chosen occupation. That is no excuse, however, for using federal funds to accommodate a researcher's own personal ambitions. Federal funds should be used only for the most promising health research needs, and only where there is not already an adequate number of qualified researchers pursuing the matter.

H. *Research priorities should not be allowed to be influenced by traditional academic views about important research issues.* Some scientific fields are regarded by the academic community as important intellectual challenges, and others are regarded as the backwaters of scientific inquiry. Academic leaders routinely advise their brightest protégés on the areas to pursue and those to avoid, for a successful academic career. The academic view of the relative significance of research subjects often bears little or no relationship to the actual health benefits that might be obtained from them. The policies that guide federal funding of health science research should be determined solely by the potential for public benefit rather than intellectual stimulation and academic honor. Targeted funding will do much to assure that barriers to important research on neglected areas are overcome.

I. *The academic emphasis on "publish or perish" leads a researcher to waste great amounts of time on trivial papers designed primarily to lengthen his curriculum vitae.* Anyone who has ever read the lengthy list of publications that routinely accompanies a research scientist's curriculum vitae inevitably wonders how many of those papers have real significance, and how many were pursued in order to assure academic tenure. The honest scientist will admit that his important and productive papers are few in number.

The proliferation of scientific publications threatens to drown the scientific community in a flood of useless information. Reducing the number of scientific journals and limiting their contents to reports of truly significant experiments would not only improve the ability of scientists to keep abreast of significant developments but would also do much to discourage unnecessary experiments that are unlikely to be of any public benefit.

J. *Federal funding of research should be based on the merit of the proposal, not on the reputation of the researcher and the institution.* Not every idea that comes from an elite institution or a well-known researcher merits support. Proposals should be reviewed initially with names of both the individuals and the institutions involved omitted so that the actual research proposal can be considered and rated on its own merit in relation to public health priorities apart from those other factors. The ability of the researcher and the facilities of the institution can then later be taken into account separately. This will permit more objective evaluation of research proposals.

K. *Most research is improperly directed toward obtaining a greater knowledge of scientific issues rather than toward rapid application of research information to solve immediate and pressing public health problems.* This country presently has an enormous wealth of basic health science information that could either immediately or in the near future be put to use to alleviate a great many public health problems. Too often basic scientific research has been conducted as an end in itself, with the result that the practical aspects that could be of great benefit to the public have been obscured or lost.

Federal research institutions currently have little or no interest in applied research as contrasted with basic research. Scientific reputations, academic tenure, and Nobel prizes depend upon the latter, not the former. The federal government must therefore either reorient the basic structure and mandate of its research institutions, or develop new institutions that will fill the current gap and shorten the time between discovery and practical application. It is essential that a major portion of the funds currently directed toward basic research be diverted instead to assuring rapid "technology transfer" to meet the nation's health needs. The public should be spending its funds not for scientific information, but for the ultimate public health benefits that will result from it.

L. *The total lack of coordination on research policy within the federal government results both in duplication of work under federal funds and in promising leads falling through the cracks.* There is no central repository for information on health science research being undertaken or funded by the federal government. Federal research agencies frequently have no information on what other researchers inside or outside the government are doing. A central coordinating function to disseminate information on current research is badly needed.

Rapid dissemination of information about research projects is impeded by the highly competitive and secretive nature of academic health science research. To the extent that federal funds are used in conducting research, any form of secrecy is wholly unjustified and should be forbidden.

M. *Researchers are more interested in the stability and continuity of research funding than in the relevance of their work to the public health and welfare.* Scientists continually complain that, if they cannot depend upon a stable and continuous source of federal funding, their work will be seriously impeded.

Long-term research projects in the federal government, and grants to outside researchers, provide at least a short-term stability that is the envy of many others in society who must be concerned about their economic welfare on a daily basis. Business and individuals can suffer severely by wholly unforeseen circumstances in the marketplace. Privately funded research conducted by industry or through other private funds is therefore constantly at the mercy of both the national economy and specific economic forces that may affect a particular industry, company, or individual.

It is undoubtedly important that health science research not be interrupted or impeded unnecessarily. But researchers have no greater right to economic stability, or to continued use of public funds, than any other citizens. They must therefore learn to cope with the same economic uncertainties and imponderables as the rest of society. The federal government should not hesitate to reduce the amount of funding in health science research proportionately whenever the country must reduce its other economic expenditures.

N. *Special interest groups have too often exaggerated the importance of particular health problems through adroit lobbying, resulting in inappropriate research priorities.* The "disease of the month" approach, although in disrepute, is still not thoroughly discredited. Special appeals are frequently made to the government to give inordinate recognition to a particular health problem without any attempt at an objective determination of its priority among all public health problems. Federal agencies should ignore any special appeal that fails to show its relation-

ship to the overall public burden of illness in this country, based upon objective factual determinations.

O. *Little research is directed toward substantiating the contribution of new drugs and medical devices to improvement of the public health and they are therefore approved without adequate assurance of public benefit.* The Food and Drug Administration is required by law to assure the safety and effectiveness of drugs and medical devices, but not to assess their impact on health care as a whole or on the quality of life. Too little attention has been paid to resulting increases in the cost of medical care and the loss of human dignity accompanied by use of such measures as life support systems that maintain human life for no reasonable purpose.

These are not areas of research that represent the cutting edge of health science knowledge. They are relatively mundane and are unlikely to attract significant scientific analysis without the impetus of targeted federal funding. Federal agencies should therefore divert funds from basic research fields that are well-covered and will attract major investigation to areas of this nature which have an enormous impact on every citizen but are unlikely to receive substantial scientific attention without the inducement of federal funding.

P. *Little research is directed towards substantiating the contribution of medical procedures to improvement of the public health and they are therefore adopted without adequate assurance of public benefit.* Physicians and other health professionals are authorized by law to engage in any form of medical procedure that they believe acceptable. The only present means of controlling unacceptable medical practice—malpractice litigation and revocation of the license to practice medicine—have had little effect in reducing unethical, ineffective, unsafe, and costly medical procedures. It seems doubtful that the medical profession can itself adopt an effective scheme of medical procedure assessment. Accordingly, the federal government should fund research designed to result in a systematic assessment of both current medical procedures and future medical procedures as they come into use.

Q. *Little research is directed toward ascertaining, much less reducing, the cost of health care to the public.* Although Congress and the public are most concerned about the rapid escalation of health care costs, health services research is underfunded, the subject of little interest. Without substantial federal support of this type of applied research—at the expense of basic health science research, if necessary—the country will reach a crisis on health care costs that will dwarf all other health science issues and could result in major reductions in federal spending for basic health science research.

The cost of health care is not presently the concern of any federal research or regulatory agency. Health science research has left this area to economists and policy-makers without adequate thought of its impact on the public. Federal agencies should make certain that in the future cost considerations are taken into account in basic health science research to the same extent that they must be reflected in the policy options available to the health care system as a whole.

R. *Little research is directed to issues of life style and behavior that have by far the greatest impact on public morbidity and mortality.* Even the most obscure disease, which affects only a handful of individuals, receives greater research attention than do the most widespread and important aspects of personal life style and behavior that affect an individual's health. The public health consequences of diet, exercise, sleep, and our other daily habits have long escaped the interest of

health science research. Yet the only realistic way of affecting many of the health problems that plague our society is by changing these and other personal habits, and thus the entire way that we live. Federal funding must make certain that health science research focuses strongly on these issues.

S. *Little research is directed toward ascertaining and removing the environmental contaminants and conditions that contribute significantly to human disease.* Some researchers have contended that up to 90 percent of all cancer can be attributed to "environmental" causes. We know extremely little about these causes, and very little health science research today is directed toward them. It is imperative that major research be undertaken to determine the environmental causes of cancer, to reduce those causes wherever possible, and to provide accurate information to the public on the basis of which individuals can make their personal choices that could significantly affect their chances of avoiding cancer.

T. *Little research is directed simply toward improving the quality of life in large populations whose basic condition cannot be changed (e.g., the aged and the infirm).* Regardless how much the fields of science progress in the foreseeable future, one cannot anticipate that the aging process will be halted or reversed. Since this gradual deterioration is one condition which no one can avoid, the federal government should place major emphasis on research designed to improve the quality of life as aging occurs. Much of this research will undoubtedly fall within the area of health services research, but a great deal will also fall within the behavioral sciences and some in the biomedical sciences.

U. *Basic research has made only a minor contribution to the improvement of public health in the past and is not likely to lead to major improvements in the future.* Recent information has shown that morbidity and mortality have substantially decreased because of such general factors as genetic selection, improved nutrition, hygienic engineering, and an overall improvement in basic societal conditions, rather than as a result of increased scientific information attributed to health science research. Further improvements in the future are likely to come from similar societal sources. Federal funding of health science research should therefore be reduced substantially or eliminated, and these funds should in the future be devoted instead to reducing poverty, the main source of health problems in this country.

II. The Public Should Have Greater Control Over, and Protection From, Health Science Research

A. *Health science researchers have no constitutional, legal, or moral right to federal funds.* The use of tax money for health science research is solely within the discretion of the general public. Accordingly, the public may attach any conditions that it wishes to the use of federal funds for health science research, and may change those conditions or reduce or eliminate such finding at any time for any reason it believes to be sufficient. Once a health science researcher agrees to accept federal funds, he also agrees to accept, and to abide by, whatever requirements and conditions are attached to those funds no matter how ill-advised or arbitrary they may seem.

B. *The role of scientists should be limited to conducting the type of research that the public concludes to be relevant to its needs (like the role of generals in conducting wars).* The public is not interested in funding health science research that is merely of

academic and intellectual significance. It wants research that is conducted with its money to be of direct and immediate importance in alleviating the nation's serious health problems. Accordingly, the lay public should have the controlling voice in determining what type of health science research should be undertaken. Scientists must then pursue those general areas of interest if they choose to use federal funds to support their research.

This does not mean that scientists in general would be restricted in their freedom of inquiry. Any scientist should be free to conduct, with his own or other private funds, any type of health science research that interests him (as long as it does not pose a danger to the public).

C. *Freedom of scientific inquiry exists only with respect to thought, not with respect to any investigation or action that may affect any person.* Any aspect of scientific inquiry that extends beyond pure thought and writing is therefore fully subject to public regulation and control to prevent potential harm. In this respect, academic research, whether basic or applied, stands on no different footing than commercial research.

D. *Researchers attach too little importance to the protection and the privacy of human subjects.* Examples of unethical human experimentation have been documented in both the scientific literature and congressional hearings. It is therefore apparent that regulatory control mechanisms must be established to protect the public from unethical and improper health science research and to assure that the privacy of those individuals who participate as subjects of such research is securely protected.

E. *The public must be protected from medical procedures which are of unproven safety and effectiveness.* Federal regulation of human experimentation with medical practice and procedures is as important as federal regulation of human experimentation with investigational drugs and medical devices. New laws must be enacted to assure appropriate public control of existing medical procedures whose uses have never been adequately supported and any new medical procedures that may be considered in the future.

F. *Even basic nonclinical research today is involving work that threatens the health of laboratory workers and the general public and therefore requires new governmental controls.* To the extent that basic research in health science may pose dangers to laboratory workers or the public, either directly or indirectly, it should be subjected to appropriate public control through federal regulatory mechanisms.

G. *The present peer review procedure is nothing short of an "old boy" system designed to perpetuate established ideas and institutions and to resist innovations that challenge accepted procedures.* Public participation is essential in the determination of which research proposals have the greatest potential for meeting public health needs. Younger scientists, and those who represent less-established concepts, should also be included in the process. Peer review should become a truly open and public mechanism for determining which proposals better suit national needs, rather than the closed and academic exercise that presently exists.

H. *The present peer review system permits review committee members to make awards to each other's institutions while pretending to avoid conflicts of interest.* It is simply insufficient for peer review committee members to absent themselves from a meeting where a grant to their institution is considered. Steps must be taken that will preclude the type of continuous conflict of interest that arises

today. Individuals must be found to serve on peer review committees who have no direct or indirect interest in the outcome of the deliberations of those committees.

I. *The secret meetings of a review committee, where a scientist who has applied for a grant is discussed without his being present and the grant can be denied without the deciding factors being revealed, is undemocratic and denies due process of law.* At the very minimum, any person who is applying for a grant should be permitted to attend any meeting, and to obtain any memoranda and correspondence reviewing that grant application. Criticism both of an individual's ability and of the merits of a research proposal should be made in front of the individual involved, and the individual should be given an opportunity to respond.

The present method of holding secret meetings, without the applicant being present, allows these important matters to be decided on the basis of conjecture, unsubstantiated opinion, and misinformation. Fundamental principles of fairness require that the applicant be permitted to correct any misimpressions or misinformation that may arise.

The failure of the National Institutes of Health to open up review committee meetings to closer public scrutiny makes it look as though the scientific establishment is trying to hide things. Only by allowing the public to know what is taking place in these meetings can the rights of the individual applicants and the broader interests of the public be protected.

III. Federal Funding of Training for Health Science Research Is an Inappropriate Use of Tax Funds

A. *Many graduate students trained with federal funds have available sufficient private funds to support their training.* At present, federal funds for research training are awarded solely on the basis of the ability of the individual, regardless whether that individual has available other funds that could be used to finance that training. The richest and the poorest receive the same amount of money.

Students often have parents who have supported them through college and spouses who can work, or they have access to private sources of funds, such as savings accounts, trusts, insurance policies with cash value. Moreover, there is no rationale for different criteria for financial assistance at the graduate level than at the undergraduate level, where scholarship funds are almost always awarded on the basis of demonstrated financial need.

B. *Many researchers trained with federal funds subsequently earn incomes that make it reasonable to require them to bear the costs of their own training.* Scientists are not notoriously underpaid. Many rise to high positions in government and in industry. Those who perform particularly useful functions for society receive ample financial reward. Those whose contributions to society are small should not receive any greater financial reward than those contributions justify.

Accordingly, all researchers, including those in financial need, should bear the cost of their own training. This can be done through a wide variety of mechanisms, such as ordinary bank loans or by the traditional American way of paying for their education by working nights and weekends. People who do not have the drive to work their way through school one way or another probably do not have drive needed to make a good research scientist anyway.

C. *There is no greater justification for federal training of health science researchers than there is for federal training of lawyers, architects, or clerical personnel.* Recruitment of able personnel in other occupations is as important to national goals as recruitment of able personnel to work in health science research. The structural soundness of buildings and the fairness of our laws are just as important to society as the maintenance of health.

Professionals in occupations other than health science research are routinely required to support their own training at the graduate as well as the undergraduate level, except for cases of financial need. A democracy cannot countenance an inequitable system under which special federal subsidies are given to graduate students in health science research while graduate students in many other equally important professions not only have no possibility of obtaining the same benefits but indeed must pay taxes to support those other graduate students.

D. *Federal support of health science research projects provides indirect federal funding of research training and thus is sufficient to continue to attract qualified researchers without additional funds specifically for research training.* Because the federal government spends billions of dollars each year on all aspects of health science research, large numbers of people have been, and will continue to be, employed in the conduct of that research throughout the country. Because such research grants and contracts indirectly provide training support for the younger research personnel working on those projects, additional federal funding of health science research training is unnecessary and should be discontinued.

E. *Those institutions which have lost federal training funds for health science research in the past few years have found alternative sources of funds.* The federal government is not the sole source of money for research training. State funds, money from private foundations and industry, and, perhaps most important, the tuition paid by students, are alternative sources for financing research training.

A number of educational institutions have lost federal research training funds in the past few years, without significant diminution of their research training efforts. Accordingly, there can be no justification for continuing similar federal funding in other institutions.

F. *There is no correlation between the quality of training given to a research student and the source of funding for that training.* Those research students who work their way through school, as many have done in the past and continue to do, will get the same education as those who receive federal funding. Indeed, it is highly likely that they will come out far better people for the experience, because they are obviously much more highly motivated than those who lead a softer life on a government stipend. Those who are willing to make sacrifices for their education are showing the type of dedication to science that was once the hallmark of health science research and has been undermined by the ready availability of federal funds.

As long as training remains available for anyone who is willing to make the sacrifices to pay for it, those people who are most attracted to health science research will find a way to raise the necessary funds, and those who would just be coming along for a free ride because it costs them nothing will properly be discouraged from doing so. Discouraging hangers-on will have the additional benefit of freeing senior research scientists from unproductive administrative functions and returning them to useful work in research.

G. *There is no correlation between the quantity or quality of research product by an individual and the source of funding for his research training.* Not all of the nation's most illustrious health science researchers were trained with federal funds. No data exists to show that people who have been trained by federal funds, as contrasted with state or private funds, have a greater research output or have advanced the public health to a greater extent.

Training grants and fellowships have uniformly been awarded to the highest quality personnel. One would therefore expect that those high quality personnel—regardless whether they are trained with federal or with state or private funds—might, on the average, ultimately make a greater contribution to the public welfare. All that any such data might show is that, in fact, highly qualified people have been chosen for training in health science research under federal funding. It could not show that, absent those federal funds, the individuals would have been any less productive.

H. *Federal research training grants are undemocratic because they favor a few elite universities and discriminate against the majority of universities which could use federal funds to improve their programs.* Federal funding of research training programs might possibly be justified as "seed money" to develop strong research training programs in particular universities where other sources of funding have not materialized in the past and the program has demonstrably suffered as a result. This would recognize the national importance of research training without continuously subsidizing programs that are more properly financed through the usual form of student tuition.

The present system, however, provides a limited number of training grants to the very universities which presently have the strongest and best programs and which therefore need the funds least. This policy is creating an even wider gap between a few top research training institutions and their competitors.

Even worse, it results in a general lowering of research training standards rather than an improvement. The best research training institutions will continue their high quality even without federal funds. Those federal funds could therefore be put to better use in other institutions to improve the quality of their research training programs. The net impact would be a larger number of high quality research training programs than presently exist.

I. *Significant amounts of research training funds are used to finance the overhead of academic institutions and to purchase new equipment rather than for the research training itself.* Present regulations permit up to 25 percent of a training grant to be used for this purpose. This only makes the richest universities even richer and further exacerbates the disparities between those who are able to obtain such grants and those who cannot.

J. *A significant number of researchers trained under federal funds pursue nonresearch careers.* Whether this is because these people were simply getting a free ride and had no serious intention of engaging in a research career, or because there are too many people trained for the available positions and other careers must therefore be pursued out of economic necessity, this fact justifies immediate discontinuation of all federal funding of health science research training. At a very minimum, any person who ultimately pursues a nonresearch career should be required to pay back the federal government the full amount of the federal funds expended on his behalf (including any funds used by the training institution for administration and overhead).

K. *Federal funding has produced an oversupply of trained researchers, many of whom cannot find appropriate jobs.* This is attributable at least in part to federal funding of health science researchers, which attracts more poeple into the field than can properly be absorbed.

The number of people who should be trained in health science research depends solely upon the number of people who can be absorbed in the marketplace. In large part, this is determined by the federal health research budget. Since that budget is not likely to increase dramatically, and there is already an oversupply of trained health science researchers, any possible justification for further federal funding of health science research training is eliminated.

It is apparent, indeed, that the artificial stimulation caused by federal funding of health science research training has, by overriding the free market mechanism for manpower in this area, created a serious national problem. The current glut of qualified health science researchers is likely to remain for some years to come even if all federal funding of research training were to be eliminated promptly.

Proof of the seriousness of the current problem is readily obtained from data showing that, even with the reduction in federal funding of health science research training at the predoctoral level in the past few years, the number of such students has nonetheless been increasing. Not only does this dictate immediate elimination of all predoctoral health science research training support, but it strongly suggests that other measures must be taken actively to discourage young people from beginning a career in this area.

L. *The free enterprise market mechanism is the best means of assuring that enough (but not too many) health science researchers will be available to meet the country's needs.* Maintaining the large numbers of trained researchers for whom there are no appropriate jobs now or in the near future on a permanent life-support system consisting of an ever-increasing number of postdoctroal fellowships simply is not the solution. It seems far more beneficial to them and to society, in the long run, to let their research ambitions die so that they may go on to pursue productive careers in other endeavors. To do otherwise would be to maintain a large cadre of highly trained and qualified health science researchers in positions of limited productivity and satisfaction, with an ever-increasing backlog of these people being produced every year.

In the future, therefore, federal funding of all research training should be eliminated. There will of course be lags between the time that the market signals a need for greater or lesser quantities of research personnel, but there is no evidence whatever that this lag will be anywhere near as great as the gap that has now resulted between academic supply and market demand as a result of federal funding of research training in this area. In short, government planning here, as in so many other places, has been shown to be utterly inadequate and inappropriate.

Conclusion

Each of these criticisms, taken by itself, may well be insufficient to cause significant concern in the scientific community. Taken as a whole, however, and repeated daily throughout the country, they must be regarded very serious-

ly and given appropriate attention before they become accepted as the basis for future health science research policy.

The NAS Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel, established pursuant to the National Research Service Award Act of 1974, has begun to analyze on a systematic basis the issues raised in part III of this paper, but a great deal more work is needed before its task is completed. No systematic review of the issues raised in parts I and II appears to have been undertaken, although sporadic attempts to deal with particular aspects of those issues have been made by a wide variety of organizations and individuals.

It is unlikely that Congress or the executive branch of the government will take any action in the short run that would result in substantial change in health science research policy in this country. The scientific community therefore has an opportunity in the years ahead to pull together a complete and convincing defense of current policy, to make changes to strengthen it where appropriate, and to assure that freedom of scientific inquiry in this area will continue with undiminished vigor in the future.

June 7, 1978

Summary of Federal Recombinant DNA Legislation
95th Congress

The 95th Congress, first session, which began January 4 and ended December 22, 1977, saw the introduction of 16 bills on the topic of recombinant DNA. In addition, there were numerous proposed bills that were debated and discarded before ever being formally introduced. Four different Committees held a total of 25 hearings or mark up sessions, listening to nearly 100 witnesses.

Due to the intense interest in this area, no consensus was achieved and the discussions continued in the second session, which began January 19, 1978. Between January 19 and the date of this report, June 7, the House has held two hearings and three mark up sessions. During that time, one bill on this topic, H.R. 11192, the Recombinant DNA Act, sponsored by Representatives Harley Staggers and Paul Rogers, was introduced. In the Senate, Senator Edward Kennedy introduced his version of the Staggers-Rogers bill as amendment 1713 to S. 1217.

Thus far the Subcommittee on Health and Scientific Affairs, chaired by Senator Kennedy and the Subcommittee on Health and the Environment, chaired by Representative Rogers, have exercised primary jurisdiction over legislation involving recombinant DNA issues in their respective bodies. However, the Subcommittee on Science, Space, and Technology, chaired by Senator Adlai Stevenson, and the Subcommittee on Science, Research, and Technology, chaired by Representative Ray Thornton, have held a number of oversight hearings concerning the science policy issues involved in recombinant DNA activities and the Thornton Subcommittee, through its parent, the Science and Technology Committee, received sequential referral of H.R. 11192 on March 24, 1978.

The Commerce Committee marked up H.R. 11192 on March 14, and reported the bill, as amended, to the House on March 24. The Science and Technology Committee, following the sequential referral of the bill to them, marked it up on April 18 and reported the bill, as amended, to the House on April 21. Although no date has been set, the bill may now be scheduled for House floor action.

A substantially amended version of S. 1217, backed by Senator Kennedy, was reported out of the Committee on Human Resources on July 22, 1977. However, Senator Kennedy later withdrew his support of the bill, and it will not be acted upon further. Mr. Kennedy has introduced his version of H.R. 11192 as an amendment in the nature of a substitute for S. 1217. In view of the June 1, 1978 letter to HEW Secretary Joseph Califano from Senator Kennedy and five other Senators, it is questionable whether or not the Senate will pass DNA legislation. The letter asks the Secretary to re-examine existing legislative authorities, particularly Section 361, to determine if they could ensure extension of the NIH DNA Guidelines to everyone.

June 7, 1978

FEDERAL DNA LEGISLATION-95TH CONGRESS
THROUGH JUNE 7, 1978

BILLS AND RESOLUTIONS

House

Bill	Chief Sponsor	Date
H. Res. 131	Richard Ottinger (D-N.Y.)	1/19/77
H.R. 3191 (Identical to S. 621)	" " "	2/7/77
H.R. 3591 (" " "	" " "	2/16/77
H.R. 3592 (" " ")	" " "	2/16/77
H.R. 4232	Stephen Solarz (D-N.Y.)	3/1/77
H.R. 4759	Paul Rogers (D-Fla.)	3/9/77
H.R. 4849 (Identical to H.R. 4759)	" " "	3/10/77
H.R. 5020 (Identical to S. 621)	Ottinger	3/14/77
H.R. 6158 (Administration bill)	Rogers	4/6/77
H.R. 7418	"	5/24/77
H.R. 7897	"	6/20/77
H.R. 11192	Rogers and Harley Staggers (D-W.Va.)	2/28/78

Senate

S. 621	Dale Bumpers (D-Ark.)	2/4/77
S. 945	Howard Metzenbaum (D-Ohio)	3/8/77
S. 1217 (Administration bill)	Edward Kennedy (D-Mass.)	4/1/77
S. 1217 (As reported: accompanied by Report 95-359)	" " "	7/22/77
S. 1217 (Amendment 754 in the nature of a substitute)	Gaylord Nelson (D-Wisc.)	8/2/77
S. 1217 (Amendment 1713 in the nature of a substitute)	Kennedy	3/1/78

June 7, 1978

FEDERAL DNA LEGISLATION-95TH CONGRESS
THROUGH JUNE 7, 1978

HEARINGS AND MARK UPS

House

Subcommittee on Health and the Environment[1]	3/17/77
" " " " " "	3/18/77
" " " " " "	3/19/77
" " " " " "	5/3/77
" " " " " "	6/7/77
" " " " " "	6/8/77
" " " " " "	6/10/77
Committee on Interstate and Foreign Commerce[1]	10/12/77
" " " " " "	10/18/77
" " " " " "	3/14/78
Subcommittee on Science, Research, and Technology[2]	3/29/77
" " " " " "	3/30/77
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" " " " " "	9/8/77
" " " " " "	4/11/78
" " " " " "	4/13/78
Committee on Science and Technology[2]	4/18/78

Senate

Subcommittee on Health and Scientific Research[3]	4/6/77
Committee on Human Resources[3]	6/16/77
Subcommittee on Science, Technology, and Space[4]	11/2/77
" " " " " "	11/8/77
" " " " " "	11/10/77

1) Chaired by Representative Paul Rogers (D-Fla.), the Subcommittee is part of the Interstate and Foreign Commerce Committee which is chaired by Representative Harley Staggers (D-W. Va.)
2) Chaired by Representative Ray Thornton (D-Ark.), the Subcommittee is part of the Committee on Science and Technology which is chaired by Representative Olin Teague (D-Texas).
3) Chaired by Senator Edward Kennedy, the Subcommittee is part of the Committee on Human Resources which is chaired by Senator Harrison Williams (D-N.J.).
4) Chaired by Senator Adlai Stevenson (D-Ill.), the Subcommittee is part of the Committee on Commerce, Science, and Transportation which is chaired by Senator Howard Cannon (D-Nev.).

June 7, 1978

FEDERAL DNA LEGISLATION-95TH CONGRESS
THROUGH JUNE 7, 1978

Summary of Bills and Resolutions

H. Res. 131: This resolution proposes that the Secretary of HEW regulate recombinant DNA activities through use of section 361 of the PHS Act. Section 361 pertains to the prevention of the spread of communicable disease.

S. 621: This bill would require the Secretary of HEW to regulate recombinant DNA research. A license for each project, issued by the Secretary, would be mandatory. The penalty for a willful violation would be a fine of up to $10,000, imprisonment for up to one year, or both. Liability for harm would be imposed without regard to fault. No patents would be allowed unless the NIH Guidelines had been strictly adhered to and full disclosure of the process made.

H.R. 4232: This bill would establish a temporary, one-year study commission to make a report on recombinant DNA issues.

S. 945: This bill would require the Secretary of HEW to regulate recombinant DNA research. The NIH Guidelines would serve as the scientific standards. The penalty for a violation would be a fine of up to $10,000, imprisonment for up to one year, or both. The penalty for a willful violation would be a fine of not less than $10,000, imprisonment for not less than one year, or both. The bill would also establish a temporary, 27-month study commission to make a report on recombinant DNA issues.

H.R. 4759: This bill would require the Secretary of HEW to regulate recombinant DNA research. The NIH Guidelines would serve as the scientific standards. A license for each facility, issued by the Secretary, would be mandatory. The penalty for a violation would be a fine of up to $1,000. There would be a limit of ten P-4 centers. State/local governments would be able to impose their own requirements if they were at least as strict as the comparable Federal standards.

H.R.6158: This is the Administration bill and was introduced in the Senate as S. 1217. The bill would require the Secretary of HEW to regulate recombinant DNA activities. The NIH Guidelines would serve as the scientific standards. A license for each facility, issued by the Secretary, would be mandatory. The penalty for a violation would be a

fine of up to $5,000. The penalty for a willful violation would be a fine of up to $5,000, imprisonment for up to one year, or both. State/local governments would be able to impose their own requirements if they were at least as strict as the comparable Federal standards.

H.R. 7418 — This bill would require the Secretary of HEW to regulate recombinant DNA activities. The NIH Guidelines would serve as interim standards. A license for each facility, issued by the Secretary, would be mandatory. Local Biohazards Committees would be established to review each project and all license applications. A National Advisory Committee, with several operational mandates, would also be established. The penalty for a violation would be a fine of up to $50,000. The penalty for a willful violation would be a fine of up to $50,000, or imprisonment for not more than one year, or both. State/local governments would be able to impose their own requirements if the requirement is necessary to protect health or the environment and is required by compelling local condition.

H.R. 7897: — (As reported by the Subcommittee on Health and the Environment). This bill would require the Secretary of HEW to regulate recombinant DNA activities. The NIH Guidelines would serve as the interim standards. A license for each facility, issued by the Secretary, would be mandatory. Local Biohazards Committees would be established to review each project and all license applications. The penalty for a violation would be a fine of up to $5,000. The penalty for a willful violation would be a fine of up to $50,000, imprisonment for not more than one year, or both. A National Advisory Committee, with some operational functions, would be established. State/local governments would be able to impose their own requirements if the requirements were necessary to protect the local health or the environment. A temporary, 2-year study commission would be established to make a report on recombinant DNA issues.

S. 1217: — (As reported by the Committee on Human Resources). This would establish an 11-member, free-standing commission to regulate recombinant DNA activities. A license for each facility, issued by the Commission, would be mandatory. Institutional Biohazards Committees would be established to approve each project at a licensed facility. The penalty for a violation would be a fine of up to $10,000. State/local governments would be able to impose their own requirements if the requirements were stricter than the comparable Federal standards and were "material and relevant" to local health and environmental concerns. The Commission would, within two years, study and report on recombinant DNA issues.

S. 1217: (Amendment #754: an amendment in the nature of a substitute for S. 1217). This bill would require the Secretary of HEW to regulate recombinant DNA activities. The NIH Guidelines would serve as the interim standards. A license for each facility, issued by the Secretary, would be mandatory. Local Biohazards Committees would be established to review each project and all license applications. The penalty for a willful violation would be a fine of up to $2,000. A National Advisory Committee would be established. Other Federal agencies would need the permission of the Secretary before promulgating any regulation in this area. State/local governments would be able to impose their own requirements only if the Secretary granted such permission and if the requirement were stricter than the comparable Federal standard, were necessary to protect health or the environment, and were required by compelling local conditions.

H.R. 11192: (As reported by the Science and Technology Committee). This bill carries over several provisions of H.R. 7897 but is much briefer. It is a two-year bill that would require the Secretary of HEW to regulate recombinant DNA activities. The NIH Guidelines would serve as the interim standards. The Secretary would be authorized to exempt projects from the Guidelines in specific circumstances. Institutional Biosafety Committees would be established to review and monitor projects. The penalty for a violation of the Act would be a fine of up to $5,000 and/or withdrawal of financial assistance. State/local governments would be able to impose their own requirements if the requirement were necessary to protect the local health or the environment. A temporary, 30-month study commission would be established to report on recombinant DNA issues.

S. 1217: (Amendment #1713: an amendment in the nature of a substitute for S. 1217). This bill is quite similar to H.R. 11192. The major difference is that S. 1217, amendment 1713, contains no provision for the preemption of State/local regulations.

United States Senate

WASHINGTON, D.C. 20510

June 1, 1978

The Honorable Joseph A. Califano, Jr.
Secretary of Health, Education and Welfare
Department of Health, Education and Welfare
Washington, D.C. 20201

Dear Mr. Secretary:

Since 1976 four committees of the House and Senate have held nine series of hearings to consider the issues relating to recombinant DNA research. These extended and thorough inquiries have shown that, with respect to the research they support and conduct, the National Institutes of Health have taken a properly cautious approach by prohibiting certain presumably hazardous experiments, requiring certification of the safety of host-vector systems, prescribing physical and biological containment measures for the conduct of permissible experiments, and providing for changes in these restrictions as further scientific evidence resolves the uncertainties about the health and environmental effects of using recombinant DNA techniques.

Evidence accumulated in the past year, rather than revealing any hazards associated with these experiments, points to a high level of safety in the use of the predominant host organism, the K-12 strain of E. coli. The NIH Recombinant DNA Molecule Program Advisory Committee has recommended changes in the Institute's research guidelines to reflect this evidence, and these recommendations are being considered by Director Fredrickson. Other hosts and vectors have received less scrutiny, and uncertainty remains about risks that may be associated with future applications of the technology. These uncertainties justify continuing to require certain precautions in recombinant DNA work.

However, the hearings have also underscored the need to correct deficiencies in the present system of regulation. Privately supported research activities are not subject to monitoring by NIH nor to sanctions for failure to comply with the guidelines. Application of the NIH standards by other Federal agencies is voluntary. As Director Fredrickson has stated on several occasions, it is doubtful this enforcement by the principal Federal sponsor of recombinant DNA research -- NIH -- is appropriate. Procedures for revising the standards and exempting certain experiments should be clarified. It is important to ensure the accountability of institutions and investigators, particularly if they are to assume greater responsibility for monitoring

ES/NIH Distr., 6/5/78: Fredrickson, Stattan, Perpich, Talbot, Gartland, OLA

NOTE: CS Distr., ASL for sec. sig.

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compliance. The Federal Government should anticipate commercial applications of recombinant DNA techniques and the concerns they are likely to raise.

In view of these developments and in view of the heavy legislative schedule of the Senate and the Human Resources Committee, we are writing to inquire whether the deficiencies in the present regulatory system can be remedied through executive action in the event final agreement on legislation is not possible. Specifically, it would seem possible to shift monitoring and enforcement responsibilities from NIH to a more appropriate agency within the Department of Health, Education, and Welfare. It would also seem possible to remedy the problems of accountability and of coverage in the process of revising the recombinant DNA guidelines. On the basis of the survey of existing statutory authorities conducted by the Committee on Commerce, Science and Transportation, there seems to be adequate authority to regulate the commercial application of products developed through recombinant DNA technology. There is, however, need for more effective coordination among Federal agencies in the implementation of these authorities.

In this regard, you expressed to Senator Stevenson in your letter of February 27, 1978, that the Food and Drug Administration "...could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the NIH guidelines on recombinant DNA." You noted also that FDA has authority to inspect firms making such certification to assure compliance with the NIH guidelines. This statement is important because most, if not all, recombinant DNA research by the private sector is being conducted by pharmaceutical companies with the objective of developing products that would be marketed in accordance with FDA regulations. A decision by the Administration to use this existing authority would bring the large majority of privately funded recombinant DNA research activities under the NIH guidelines. Is the Administration prepared to use the authority cited in your February 27th letter?

Finally, it has been suggested that section 361 of the Public Health Service Act provides sufficient authority to promulgate regulations covering recombinant DNA research conducted by the private sector with non-Federal funds. Although you have expressed the view that specific legislative authority is preferable to using the authority of section 361, we are raising the issue again for three reasons: (1) the need for new legislation is less clear than it was one year ago when the initial bills were introduced, (2) the existing

regulatory deficiencies relating to Federally-supported research can be remedied by executive action, and (3) the heavy legislative schedule may preclude action in this session of Congress. In view of these developments, it seems prudent to explore the willingness of the Executive Branch to use the authority of section 361 to cover privately-funded recombinant DNA research. In addition, we request that you solicit a legal opinion from the Department of Justice as to the use of section 361 in this manner.

There is an additional factor to consider. In the past, Congress has been reluctant to extend statutory control over a specific field of scientific investigation unless such authority was absolutely necessary to protect the public's health and safety. In view of the scientific evidence accumulated during the past year, it is not possible to reach this conclusion in the case of recombinant DNA research. If the deficiencies discussed above could be corrected through executive action -- by use of existing powers of FDA and/or the authority of section 361 -- there would be no reason to legislate new statutory controls.

In the event these executive actions were implemented, we would recommend that an appropriate group of experts and lay persons, such as the advisory committee to the NIH Director, continue to monitor the scientific evidence relating to the hypothetical risks of recombinant DNA research. If evidence indicating actual risks were to be developed, Congress could once again consider the need for legislation.

Since we are presently considering the legislative agenda for the balance of this session, we would appreciate your prompt response to this inquiry.

Sincerely,

EDWARD M. KENNEDY, Chairman
Subcommittee on Health
and Scientific Research

ADLAI E. STEVENSON, Chairman
Subcommittee on Science, Technology
and Space

JACOB K. JAVITS, Ranking
Minority Member
Committee on Human Resources

HARRISON A. WILLIAMS, JR., Chairman
Committee on Human Resources

GAYLORD NELSON, Member
Committee on Human Resources

RICHARD S. SCHWEIKER, Ranking
Minority Member
Subcommittee on Health
and Scientific Research

SUMMARY MINUTES OF
DIRECTOR'S ADVISORY COMMITTEE MEETING
DECEMBER 15-16, 1977

Introduction to the Meeting

Dr. Donald Fredrickson, Director of the National Institutes of Health, opened the meeting with a brief prologue. He noted that the Guidelines for Recombinant DNA Research were published in June 1976, the draft Environmental Impact Statement in September 1976, and the final Environmental Impact Statement in November 1977. Dr. Fredrickson pointed out that the Guidelines were constructed in response to concerns about the possible hazards of recombinant DNA research. He added that this area of science is rapidly evolving with new information continuously coming to light. The Guidelines would need to be a living document in order to respond.

Dr. Fredrickson stated that NIH has taken seriously the duty to preserve due process and to provide for public participation in the first revision of the Guidelines. The proposed revised Guidelines have been published in the Federal Register and the NIH Recombinant Technical Bulletin (Fall 1977). The revisions are based on new scientific and administrative experience. They anticipate the possibility of legislative developments. In the absence of legislation, all federally funded recombinant DNA research is being conducted under the NIH standards. Similar guidelines exist in other countries and many national committees look to the NIH for guidance.

Dr. Fredrickson continued by noting that recombinant DNA techniques and the policies governing their use can serve as a case model for public and scientific participation in developing national and international science policy. He reminded the audience that the subject of this meeting is the proposed revision of existing Guidelines and its purpose is to develop facts and opinions concerning the next stage of development of the Guidelines.

Dr. Fredrickson concluded his introduction by describing the format of the meeting. The review of each relevant section would begin with a short presentation by a member of the Recombinant DNA Molecule Program Advisory Committee (RAC), followed by comments from invited witnesses and public witnesses respectively. Members of the Advisory Committee to the Director, NIH (DAC) would have the opportunity to question witnesses in a frank and open discussion of views. Towards the close of the meeting each member of the DAC would provide a brief oral summary and then follow at some future date with more detailed written comments. Dr. Fredrickson urged all interested participants to submit comments.

Introduction to the Proposed Revised Guidelines

Dr. John Littlefield (RAC) briefly described the Introduction to the Guidelines. He noted that the term "recombinant DNA" had been redefined and that the members of the RAC believed the new definition to be a workable one. The definition will exclude certain types

of experiments, particularly those in which a population of naturally recombining DNA such as bacteriophage T7 DNA or fragments of E. coli DNA will be cloned in an E. coli host. Dr. Littlefield was followed by Dr. Maxine Singer (NIH) who presented additional testimony on the definition of recombinant DNA. Dr. Singer noted that neither the current nor proposed revised Guidelines provide any guidance on containment levels for experiments that involve chemically synthesized DNA. Dr. Singer proposed wording for synthetic DNA.

In the discussion that followed, Dr. Fredrickson again noted that the RAC believed the current definition to be too inclusive and ignoring the phenomena of natural recombination. The RAC therefore introduced the concept of "novel recombinants." The RAC would be charged with the responsibility for development of a list of exemptions. Members of the DAC agreed with the concept of such a list but expressed concern over the lack of clarity in the term "normal physiological process."

The invited and public witnesses also commented on the definition of recombinant DNA and the distinction between novel and non-novel recombinants. Ms. Nancy Pfund (Sierra Club) asked what data had been used to justify the revisions made in the Guidelines. She further suggested that emphasis be placed on the concept of safety rather than novelty in categorizing recombinants and that all publications be required to list the levels of biological and physical containment

at which the experiments were done. Dr. Jonathan A. King (MIT) noted that very little information has been gathered concerning the incidence of laboratory infection, particularly as a control population for future studies of laboratories involved in recombinant DNA experimentation. Dr. Mary-Dell Chilton (University of Washington) described her research on crown gall tumors in plants. The tumors are caused by bacterial plasmids which can also be induced to grow in E. coli. Under the proposed Guideliness, by one criterion the cloning of this plasmid DNA would be eligible for the excluded list of experiments but, by another, it would not. She asked that consideration be given to resolving this disparity.

Other comments were made both about the lack of clear and explicit language in some sections of the Guidelines and about their lack of reference to regulation for the private sector. Dr. Ronald Cape (Cetus Corporation) indicated he favored passage of a law regulating private and public laboratories with the inclusion of exemptions for patent rights and trade secrets.

Physical Containment

Dr. Emmett Barkley (NIH) described the changes that had been made in the section of the Guidelines dealing with physical containment. He pointed out that there were no significant differences between the two versions except for a new format for the material and an attempt

to harmonize levels of physical containment among the various countries promulgating guidelines. Many of the revisions were based on the outcome of a NIH/EMBO sponsored workshop on containment.

Dr. Barkley indicated that three major categories had been developed. These included safer laboratory practices, such as employment of standard microbiological techniques, containment equipment, and special laboratory design. With regard to containment equipment, the P2 level requires the use of biological safety cabinets in certain experiments, the P3 level requires biological safety cabinets for all experiments, and the P4 level requires the use of glove boxes. Special laboratory design at the P3 level requires access control, directional air flow and surface treatment, and at the P4 level requires facility isolation, a change room, sealed surfaces and a secondary treatment system.

Dr. Barkley noted that the safety of the individual worker depends primarily on laboratory practice and the use of containment equipment while environmental protection depends upon all three elements. Current NIH designations for increasing levels of physical containment adhere closely to the equipment and special laboratory design criteria described by the NIH/EMBO Workshop. Revisions in the Guidelines incorporate laboratory design recommendations and new mandatory requirements for safe biological practices.

A number of comments were made both by members of the DAC and by the various public witnesses. Dr. Sinsheimer (DAC) pointed out

that lowered physical containment for a given class of experiments could increase the number of laboratories where the experiment takes place and consequently increase the possible hazard. There was particular concern about the need for training in microbiological techniques. In response to a question about release of untreated air from P3 level laboratories, Dr. Barkley noted that all air expelled from inside the biological safety cabinets is filtered prior to release while only the air from the normal laboratory environment is vented directly.

Biological Containment

Dr. Sue Gottesman (NIH) presented the RAC rationale for revisions in the area of biological containment. She noted that the use of enfeebled hosts and vectors would both limit the potential for survival of the host and for transmission of the vector. The best examples are the development of χ1776, a strain of E. coli K-12 which can only survive in a very permissive set of laboratory conditions and the creation of vectors with host dependent mutations, such as bacteriophage lambda which contains amber mutations and can only grow in a supressor host.

Dr. Gottesman described the HV nomenclature and its application as a general host-vector designation. The only HV1 system now in existence is EK1, although if other certified hosts are to be used experiments should only be conducted at the P2 level with non-pathogenic

prokaryote genes. Any further experiments to be conducted with that HV1 system would require explicit approval by the RAC. Similarly, E. coli host-vector systems (EK) are the only candidates for HV2 and HV3 certification. For certification at the HV3 level the vector must be host dependent or defective in mobilization and, if a plasmid, not contain markers conferring resistance to antibiotics used clinically or in agriculture. Dr. Gottesman further noted that other HV2 and HV3 systems can be considered as they are developed; and that testing of such systems would in the process create better performance criteria for their final evaluation and certification. Similarly, the designation of a system as HV3 would not necessarily inhibit its risk assessment since each candidate could include a marker that would permit assay of its presence during in vivo testing.

In the discussion that followed Dr. Gottesman's presentation, Dr. Fredrickson indicated that other types of risk assessment experiments in addition to testing and evaluation of HV2 and HV3 systems could be specifically exempted from the provisions of the Guidelines. In a related comment, Dr. John Tooze (EMBO) stated that the polyoma DNA risk experiment proposed by NIH was being already carried out in Europe. Polyoma DNA lambda hybrids had been constructed, were currently being characterized, and would be given to mice. Dr. Tooze pointed out that containment levels for cloning of viral DNA in Europe are less stringent than those in the United States.

Questions were raised by the public witnesses regarding the adequacy of the data employed to certify HV2 and HV3 systems. Concerns were expressed that all tests and performance criteria be made a matter of public record so that comments could be received prior to certification of a given system. Recommendations were also made concerning the need for more extensive risk assessment studies, including those employing statistical analyses, and for NIH certification of HV systems developed by industry.

Experimental Guidelines

The justification for the proposed revisions in the Experimental Guidelines section was presented by three members of the RAC.

Dr. Donald Helinski described changes in containment levels for prokaryote and eukaryote DNA. He noted that the list of prohibited experiments has not been altered although the revised Guidelines do have a provision for exemption of specific experiments in each class. In the permissible class, most experiments will use E. coli K-12 as the host, although other HV1 Systems can be employed. Many categories have not been changed and are, in fact, even more stringent due to more rigorous requirements for certification of host vector systems. As examples of experiments that can be conducted at lower containment levels, Dr. Helinski mentioned shotgun cloning into E. coli K-12 of both non-primate mammalian DNA (from P3 + EK2 to P2 + EK2) and primate DNA (from P4 + EK2 to P4 + EK1). He pointed out that the proposed new definition of

recombinant DNA will eliminate regulation of experiments with prokaryote DNA cloned into E. coli K-12 where the organisms normally exchange genetic information with E. coli K-12.

Dr. Helinski then summarized the results from a series of published and unpublished experiments that the RAC believed justified its decision to lower containment levels. A recent conference held on risk assessment indicated that E. coli K-12 could neither be converted to a pathogen nor could it colonize the normal human gut. The variant strain χ1776 could not even be established in germ free mice. Other data indicated that plasmid transfer in the intestines was infrequent and required the use of conjugative plasmids, and the narrow host range of phage vectors markedly limited their transmissability. Dr. Helinski went on to present evidence that exchange of genes can occur in nature in normally nonexchanging species. Finally he described experiments in which plants have been shown to take up bacterial DNA and alternatively in which eukaryotic DNA has been taken up by bacterial cells and incorporated in the host genome.

Dr. Helinski then responded to questions from the DAC. He noted that decisions on exceptions to prohibited experiments would be made by the Director, NIH on the recommendation of the RAC. He also pointed out that experiments were underway to assay for the possibility of plasmid escape through the sewage system or

by transduction to another bacterium. Dr. Helinski indicated that in terms of approximating physiological conditions in a test tube, the mild shock treatment employed to facilitate transformation in E. coli was not that far from the norm. Similar levels of calcium, for example, are found in the intestinal tract.

Dr. Helinski was followed by Dr. Rowe who presented the RAC recommendations on viral DNA. Dr. Rowe briefly described the various classes of viruses including retroviruses (which carry reverse transcriptase), baculoviruses (DNA viruses that infect insects), and papova viruses (which include SV-40 and polyoma). Dr. Rowe described the containment levels required for viral DNA.

A considerable discussion ensued with DAC members asking why viral DNA required such high containment levels. Dr. John Tooze (EMBO) contrasted the European attitude toward cloning viral DNA. He first pointed out that many European countries had adopted guidelines but had not felt it necessary to pass laws. In each country, each virus cloning proposal is put forth to a national committee and is judged individually. He noted that when viral DNA such as SV-40 or polyoma is used as a vector it will pick up host DNA by natural recombination, so that to clone mouse DNA via polyoma in mouse cells at a P3 level does not seem justifiable.

Dr. Zaitlin concluded the section on Experimental Guidelines by discussing changes suggested for plant DNA. Dr. Chilton (University of Washington) testifying as an invited witness suggested that the

Guidelines should reflect differences in the virulence of individual plant pathogenic bacteria with a general level of P2 + EK2 for cloning in E. coli K-12. She stated that to her knowledge the only plant pathogen bacterial DNA currently being cloned is the tumor inducing DNA of Agrobacterium tumifaciens which is now at P2 + EK2 but in the revised Guidelines would be either at P3 + EK2 or not restricted at all. A final point was made by Leslie Dach (Environmental Defense Fund) who asked for a better rationale in the Experimental section for the categorization of certain classes of experiments into specific physical and biological levels.

Roles and Responsibilities

Dr. Fredrickson introduced this section by noting that the Guidelines refer to NIH grantees but are also subscribed to by the NSF and USDA. He believed that the Guidelines will continue to evolve as more groups come under their aegis. Dr. Fredrickson then asked Dr. William Gartland (ORDA) to provide a chronology of events for the implementation of the Guidelines. Dr. Gartland indicated that prior to promulgation of the Guidelines in June 1976, NIH sent letters of information to its grantees which stated that guidelines were under consideration and asked each principal investigator to return a statement of agreement to abide by the Asilomar guidelines. Following publication of the NIH Guidelines, ORDA sent notices to both institutions and principal investigators establishing procedures

of compliance including creation of institutional biohazards committees and memoranda of understanding and agreement (assurance of familiarity and compliance with the Guidelines) and subsequently requiring prior approval from NIH for all new, or continuing research activities involving recombinant DNA technology. ORDA also developed procedures designed to facilitate processing of the documents by NIH staff.

Dr. LeRoy Walters (RAC) then described the proposed changes in the Roles and Responsibilities section. The RAC recommended that; 1) institutional biohazards committees include individuals who represent community involvement 2) institutions with P3 and P4 level experiments appoint a biological safety officer who would have oversight functions, 3) certification of host-vector systems proceed through a mechanism including review by an expert subcommittee of the RAC, concurrence by the RAC, and final approval by the Director, NIH, who would have ultimate responsibility, and 4) an administrative mechanism be developed for exemptions to the Guidelines in which a procedure similar to certification would apply. In discussion with members of the DAC, Dr. Walters indicated that the Guidelines do not address the question of voluntary compliance for non-governmental funded research.

The public witnesses addressed the issue of enforcement. Representatives of the AFL-CIO indicated that although the Guidelines have set standards for good personnel practices, they believed that the Occupational Safety and Health Administration (OSHA) had

the responsibility for enforcement. They disagreed with the concept of voluntary compliance citing the lack of evidence in other areas for such willingness by American industry. They believed regulations with provisions for penalties were required with the final responsibility resting in OSHA. A representative of the Pharmaceutical Manufacturers Association (PMA) expressed his industry's willingness to comply with the Guidelines providing provision could be made for preservation of trade secrets. Other witnesses suggested mandating the composition of the institutional biohazard committees, public representation on the RAC, and on-site inspections by NIH when necessary.

Conclusion

In the discussion period each member of the DAC summarized his or her viewpoint. The issues addressed included training of laboratory personnel, collection of data on the incidence of laboratory infections, public representation on institutional biohazard committees, and the need for more risk assessment studies. Dr. Fredrickson closed the meeting by requesting more detailed written comments from each of the participants.

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